Abstract There is a growing interest in neoadjuvant chemo- and radiotherapy as a treatment modality for colorectal cancer which could affect mechanical and biochemical parameters of anastomotic healing. This study investigated the effect of such protocols on colonic anastomotic healing by evaluating the histopathological parameters. One hundred and sixty male Wistar rats were divided into six groups: a control group (I, n = 20), a saline group (II, n = 30) which received 1 ml NaCl intraperitoneally, a sham-irradiated group (III, n = 20), a 5-fluorouracil (5-FU) group (IV, n = 30), which received 5-FU (20 mg/kg) intraperitoneally for 5 consecutive days, an irradiated group (V, n = 40) which received fractionated irradiation to the whole pelvis to a totaldose of 22 Gy, 5.5 Gy per fraction on 4 consecutive days, and a concomitant 5-FU + irradiation group (VI, n = 20) which received fractionated irradiation to the whole pelvis to a totaldose of 22 Gy, 5.5 Gy per fraction on 4 consecutive days, and a concomitant 5-FU + irradiation group (VI, n = 20) which received 5-FU as in group IV and irradiated as in group V. All groups underwent left colonic resection with primary anastomosis, and the last fraction of irradiation and the last injection were given 4 and 3 days before the operation, respectively. Within each group one half of the animals were killed on the third postoperative day and the other half on the seventh postoperative day. After the resection of the anastomotic segments, histopathological examination was evaluated. Apposition of the wound edges of the mucosa and the muscularis were not affected by the therapy. The level of granulocytes was high, inflammatory exudate and necrosis persisted, granulation tissue formation was delayed, and the levels of macrophages and fibroblasts were low. We conclude that colonic anastomotic healing can be affected by the administration of preoperative chemotherapy, irradiation, and chemoradiation.

Key words 5-fluorouracil · Fractionated irradiation · Colorectal cancer

Introduction

Regrowth of residual cancer cells following surgical excision of rectum carcinoma is almost inevitably fatal. Various (neo)-adjuvant therapy protocols have been investigated in the effort to improve cure rates and reduce loco-regional recurrences [1–7]. Radiotherapy either alone or in combination with chemotherapy has yielded encouraging results. However, it has been demonstrated that postoperative irradiation and antineoplastics have deleterious effects on intestinal anastomotic healing [8–11].

Despite improvements in diagnosis and therapy, wound failure remains a major clinical problem. Intestinal wound healing is a complex process involving various biological, morphological, and immunological systems. Moreover, multiple extrinsic and intrinsic factors affect this healing in the gastrointestinal tract (GIT). Although the anastomosis is performed between healthy intestinal segments, it may be prone to leak or be compromised by the (neo)-adjuvant therapy. This may further increase morbidity and mortality.

Although mechanical and biochemical aspects of intestinal anastomotic healing have been reported following antineoplastics and irradiation [8–15], only very few studies have investigated the histological aspects. Since (neo)-adjuvant chemo- and radiotherapy for rectal carcinoma could affect histological parameters of wound healing, this
study assessed the early effects of such possible clinical (neo)-adjuvant treatments on colonic anastomotic healing in an experimental model similar to common clinical applications. We have recently completed investigating the effects of these possible neo-adjuvant clinical protocols on the healing of colonic anastomosis. In the present part of the study, we consider mainly the early phase of histological aspects of wound healing.

**Material and methods**

A total of 160 male Wistar rats of median weight 240 g (range 205–340 g) were used in the present study. All animals had free access to a standardized laboratory diet and water.

**Technique of irradiation and concomitant therapy**

There were six groups, (the first three of which were controls and the second three treatment groups; Fig. 1):

- **Group I**: control group (n=20)
- **Group II**: saline group (n=30), which received 1 ml intraperitoneal NaCl
- **Group III**: sham-irradiated group (n=20), which were handled similarly as the irradiation group but were not irradiated
- **Group IV**: 5-fluorouracil (5-FU) group (n=30), which received 5-FU (20 mg/kg) intraperitoneally for 5 consecutive days
- **Group V**: irradiated group (n=40), which received fractionated irradiation to the whole pelvis at a total dose of 22 Gy, 5.5 Gy per fraction through anterior and posterior fields, over 4 consecutive days with 6-MV photon beams using a linear accelerator (SL-25; Philips, Crawley Sussex, UK)
- **Group VI**: concomitant 5-FU + irradiation group (n=20), which received 5-FU as in group IV and irradiation as in group V