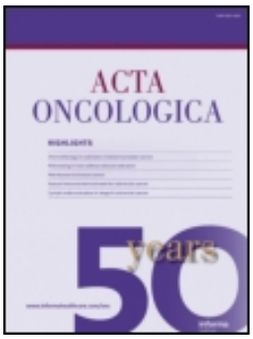

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LETTER TO THE EDITOR

Preoperative sequential short-term radiotherapy plus chemotherapy can induce complete remission in T3N2 rectal cancer

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To the editor:

In rectal cancer, preoperative short-term radiotherapy with 25 Gy administered within one week leads to significant reduction of local recurrences but no down staging because surgery is generally performed within only a few days [1–3]. For the same reason co-administration of systemic chemotherapy seems to make no sense and has not been attempted. Sequential use of both treatment modalities followed by surgery at a later time point, however, might have the same "antitumour potential" as preoperative long-term radiochemotherapy, today's probably optimal treatment choice in patients with locally advanced rectal cancer [4]. The present report describes the successful use of this novel therapeutic concept in two patients with MRI-staged T3N2 rectal cancer (located at 4 cm and 7 cm from the anal verge without distant metastases) who attended our clinic in May and July 2004. Conventional preoperative long-term radiochemotherapy was offered to them routinely. Because of personal/geographical reasons as well as financial needs, both refused this treatment strategy; they wanted to continue regular work and attend the clinic as seldom as possible. After extensive information and discussion about possible alternative treatment options, it was decided to combine short-term radiotherapy immediately followed by dose-intensified capecitabine + oxaliplatin, a combination regimen that has shown an encouraging therapeutic index in patients with metastatic colorectal cancer [5]. Both patients consented in writing to undergo this hitherto untested combination of two treatments that have been studied in different settings in this disease.

Prior to therapy, a full diagnostic workup including routine laboratory examinations, rectoscopy with biopsy, colonoscopy, thoracic plus abdominal CT, and pelvic MRI was performed. Radiotherapy was designed on the basis of a planning computed tomography with three fields covering the entire mesorectum including the tumour and lymph-nodes with a 1 cm safety margin [6]. The whole anal canal was included in the first patient, but not in the second. Single doses of 5 Gy to be administered daily to a total dose of 25 Gy were prescribed at the ICRU point. After completion of radiotherapy, chemotherapy was started on Monday of the following week. Oxaliplatin 85 mg/m^2 was administered iv on days one and 15 with usual antiemetic premedication (5-HT3 antagonist + dexamethasone), and capecitabine 3500 mg/m^2 was given orally in two divided doses from days one to seven and 15 to 21 as previously described [5]. Treatment was repeated every four weeks for three cycles. A complete restaging with thoracic and abdominal CT and pelvic MRI was scheduled thereafter, before surgery.

The first patient, a 55 year-old male, presented with about seven fecal discharges per day, permanent painful urge, incontinence for fluid stools, and the feeling of pressure at micturition. Otherwise he was in very good general condition. Upon diagnostic workup, a 7 cm long rectal cancer with infiltration of the anal canal, infiltration of perirectal tissue and multiple suspicious lymph nodes (T3N2) was found upon MRI. There was no evidence of distant

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metastases. The second patient, also a 55 year-old male, presented with irregular loose stools, abdominal pain, urge and repeated hemorrhage with anemia requiring rbc transfusion (Hb 7.7 mg/dl). MRI showed rectal cancer beginning at 7 cm from the anal verge with 9 cm cranio-caudal extension and stenosis, infiltration of perirectal tissue and multiple enlarged lymph nodes (T3N2). Again no distant metastases were detected on thoracic and abdominal CT. Radiotherapy was uneventful in both patients, no local skin reactions occurred. Urge and pain significantly decreased in both patients about two weeks after initiation of radiotherapy and the first week of chemotherapy. There was no further bleeding (in the second patient) and stool frequency dropped to about 3 to 5 discharges in both patients. Haematological toxicity included CTC-NCI grade 1 leukocytopenia and thrombocytopenia in both patients, and grade 1 anaemia in the second patient after having received transfusions before the start of radiotherapy. Both patients experienced grade 2 neurotoxicity, but continued work during treatment, one as an independent salesman travelling abroad, the other as a druggist. No other adverse reactions were recorded, and gastrointestinal symptoms continued to improve.

Restaging after completion of preoperative treatment revealed no new metastases. Pelvic MRI showed marked regression of tumour and lymph-nodes, but lesions were still detectable. Surgery was performed two weeks after the last dose of capecitabine in the first and after six weeks in the second patient. Abdomino-perineal excision with total mesorectal excision was performed in the first patient. The mesorectal tissue was edematous and showed some induration, but there were no bleeding or technical problems. In the second patient, low anterior resection with total mesorectal excision was performed also without relevant bleeding. Frozen section showed a tumour-free distal resection margin. A stapled anastomosis was performed to the distal rectum, which had to be reinforced by transanal manual sutures because of an airleak anteriorly and a diverting colostomy was done. Histological workup of both resected specimens revealed granulomatous tissue, the muscularis propria appeared destroyed, but no vital tumour cells were detected in multiple sections. The lymph nodes (eight and ten nodes, respectively) showed hyalinosis and fibrosis, but also no vital tumour cells, giving rise to complete pathological remission of tumour and lymph nodes in both cases. Patients were discharged from hospital on days eight and ten post surgery in good general condition.

Complete pathological remission (pCR) of rectal cancer prior to surgery has been achieved in 8% to 19% of patients undergoing long-term radiotherapy to 50.4 Gy combined with concomitant 5-FU or oxaliplatin plus capecitabine chemotherapy [4,7]. Achieving a pCR with an alternative treatment approach in 2/2 consecutive patients makes it unlikely to have occurred just by chance. In fact, two patients who refused to comply with conventional preoperative radiochemotherapy requiring daily hospital visits for five weeks received a combination of 25 Gy short-term radiotherapy followed by a dose-intensified capecitabine + oxaliplatin regimen which has been shown to exert encouraging response activity in metastatic colorectal cancer [5]. Both of our patients achieved a complete pathological remission and their marked initial symptoms (urge, bleeding, pain) subsided already about two weeks after the start of preoperative treatment. It is tempting to speculate that increasing the dose density of both radiotherapy and chemotherapy ± administering these treatment components in a tight sequence may add up in an intensified anticancer activity. Of course, this hypothesis remains to be investigated further. One already ascertained merit of this treatment regimen, however, is a very convenient scheduling for the patients, sparing them four weeks of daily visits to the radiotherapy department, which seems attractive also from an economical perspective. Both of our patients continued their jobs throughout therapy, also supporting its good tolerability. In conclusion, sequential preoperative radiochemotherapy, 25 Gy within one week followed by three cycles of dose-intensified capecitabine + oxaliplatin can induce complete pathological remission in stage III rectal cancer and is well tolerable on an outpatient basis. According to this data and evidence that complete remission or marked down staging after preoperative radiochemotherapy may lead to improved survival in rectal cancer [8], we decided to initiate a phase I/II study to further investigate the therapeutic potential of this promising novel treatment approach.

Declarations

There is no conflict of interest of either author. There was no special funding for this study. JW, FH and WS jointly designed the treatment approach and treated the patients.

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