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# A favourable pathological stage after neoadjuvant radiochemotherapy in patients with initially irresectable rectal cancer correlates with a favourable prognosis

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**Abstract**

Initial treatments of locally advanced rectal cancers focus on local control, as local relapse of a rectal cancer is correlated with a high morbidity and mortality. We studied the effect of neoadjuvant radiochemotherapy on advanced rectal cancer patients in relation to downstaging, local relapse and survival. Post-treatment pathological staging, local relapse and survival were analysed in 66 patients from a single institution. 43 patients had irresectable cancer as determined by laparatomy ($n=42$) or rectal examination ($n=1$). These 43 patients received 45–56 Gy preoperatively with 5-fluorouracil (5-FU) and leucovorin (350/20 mg/m$^2$×5 day (d)) in weeks 1 and 5 during the radiation therapy. 23 patients had primary resectable tumours with a T1-2 stage. Of the initially irresectable tumours 79% became macroscopically resectable, in 74% a R0 resection was performed. In 6 of 34 (18%) surgical specimens, no tumour was found (pT0), 7 patients had small tumour remnants (pT1-2). In these pT0-2 tumours, no local relapses occurred (observation period of median 4.5 years, range 18–87 months). In the 21 patients with pT3-4 tumours 3 local relapses were seen. In the 23 patients with primary resectable T1-2 tumours the relapse rate was 4%. Downstaging of an initially irresectable rectal tumour to pT2 or less results in a local relapse rate and overall survival that correspond with the rates in primary resectable cancer with the same T classification.


*Keywords:* Rectal cancer; Downstaging; Neo-adjuvant; Radiochemotherapy

## 1. Introduction

Surgery is the mainstay of treatment of patients with rectal cancer and obtaining tumour-free margins is essential for a potentially curative operation [1]. If, due to extensive growth in, or fixation to adjacent structures, such margins cannot be obtained, the tumour must be considered to be irresectable. This situation is diagnosed in approximately 10% of cases [2]. If this condition is recognised early, before definitive surgery, attempts can be made to reduce the tumour size by using radiotherapy alone or in combination with chemotherapy (neo-adjuvant treatment) [3]. If successful, this strategy leads to resectability and a pT and N classification can be determined. We have studied if the prognosis, as far as local recurrence and survival is concerned, of these downstaged tumours is comparable to that of tumours that are resectable without neoadjuvant treatment. For that purpose, clinical endpoints in 43 patients treated with neoadjuvant radiochemotherapy followed by surgery were compared with 23 contemporary patients who underwent primary resection.

## 2. Patients and methods

Over a period of 5 years until 1999, 136 patients were treated in our hospital for rectal cancer. 27 underwent palliative procedures because of metastatic disease.

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Clinical resectability was evident in 33 patients and they were treated with standard treatment: surgery alone or after 30 Gy irradiation ($n=10$). If resectability was in doubt, because mobility could not be established, patients were staged bi-manually during surgery with the patient in lithotomy position. In 33 patients, resectable disease was found during this procedure, they received standard treatment as above.

In 42 patients, the bimanual examination revealed invasion of the projected surgical margins hence the descending colon was transected to fashion an end colostomy, a hidden colostomy was made in the proximal colon [4]. In one additional patient, clinical examination before surgery established invasion in the perisacral fascia. These 43 patients were treated with combined radiochemotherapy before definitive surgery.

Preoperative treatment in these patients consisted of a combination of chemo- and radiotherapy. Radiotherapy was based on a 3 or 4-field technique. The patients were treated daily with megavoltage radiation (6–15 MV) to a volume encompassing the small pelvis. Anterior/posterior fields were custom-shaped with a 1.5 cm margin lateral to the bony pelvic inlet to cover the iliac lymph nodes. The superior border of the field was at the L5/S1 junction and inferiorly, the field was extended to the anal verge for distal cancer or 3.5-cm inferior to the distal extent of the lesion for proximal cancer. Lateral fields were shaped to include the external iliac lymph nodes with the border anterior to the symphysis, and a 1.5 cm margin posterior to the sacrum. The whole pelvis received a total of 45 Gy, with the dose prescribed to the 95% isodose line using standard fractions of 1.8 Gy/day (d) 5×/week. This was followed by a reduced field encompassing the tumour for an additional 5–15 Gy.

Radiotherapy was accompanied by 5-fluorourcil (5-FU) and leucovorin (350/20 mg/m$^2$×5d; in weeks 1 and 5 during radiotherapy). Surgery was attempted after 6–8 weeks. 21 (62%) patients underwent abdomino-perineal resection (APR), 11 patients (32%) underwent a Hartmann procedure and two patients underwent a low anterior resection. During this study period, 11 patients were entered in a prevailing protocol, with intra-operative radiotherapy with a dose of 10 Gy. A weekly dose of 5-FU and leucovorin (450/20 mg/m$^2$) for a period of 12 weeks was given postoperatively in 17 patients.

Endpoints were postoperative pathological stage, local relapse and survival. Survival of the patients was measured from the start of neo-adjuvant therapy. These results were compared with the same parameters in 23 concomitant patients with primarily resectable clinical and pathological T1 and T2 rectal cancers treated by the same team of surgeons.

7 (30%) of these patients underwent abdomino-perineal resection (APR), 8 patients (35%) underwent a Hartmann procedure and 8 (35%) patients underwent a low anterior resection (LAR). Survival was calculated using the Kaplan–Meier method [5]. The survival rates between groups were tested for significance using the log-rank test [6].

## 3. Results

From the 43 patients with irresectable tumours, 2 patients did not complete the planned treatment, due to the appearance of metastatic disease and terminal deterioration of the clinical condition. For the other 41 patients, neoadjuvant treatment was uneventful.

Only mild haematological and gastrointestinal toxicity was seen, the maximal score was a grade III anaemia (World Health Organization (WHO) common toxicity score, haemoglobin (Hb) = 4.1 mmol/l) in 1 patient. Eleven percent of the patients experienced grade II nausea and 11% grade II diarrhoea. Mucositis was minimal, only 5% of the patients had a grade I mucositis.

After preoperative chemo-radiotherapy, 34 (30 male) irresectable rectal tumours became macroscopically resectable (79%). From the 30 male patients, 8 underwent a total exenteration and 2 a partial bladder resection. In 1 female patient, posterior exenteration (uterus and posterior vagina wall) was undertaken and in 2 patients the posterior vaginal wall was excised.

The mean period between operation to discharge from hospital was 23 days (median 15, range 9–90, $n=34$). However, in 13 of the 34 patients this was more than 20 days, with a mean of 40 days (median 32, range 21–90, $n=13$). The long period of hospitalisation in these patients was due to an abscess ($n=3$), fistula ($n=6$), wound dehiscence ($n=2$), infection (central line: $n=1$; pulmonal: $n=1$), bleeding ($n=1$), cerebro-vascular accident ($n=1$). Long-term complications ($>1$ year after the resection) were erectal dysfunction in the majority of the patients and 2 patients still had fistula.

Thirty-two (74%) of the resected specimens were microscopically radical (R0). In the group of 34 patients, 6 specimens (18%) showed a pathological complete response (pT0). In 7 cases, only small amounts of vital tumour tissue were found (pT1-2). In 21 patients, limited tumour downstaging (pT3-4) was found, but the tumours became resectable. In this group (pT3-4), 9 patients had positive lymph nodes. There was a statistically significant difference in survival between the node-positive (26%) and node-negative patients ($P=0.0017$). None of the patients in the maximally downstaged group (pT0-2) had positive lymph nodes.

During the median observation period of 4.5 years (range 18–87 months), no local recurrences were found in the pT0-2 group ($n=13$). Three patients in the pT3-4 group developed a local recurrence (14%). Distant metastases where found in one patient in the pT0-2 group (liver) and in ten patients of the pT3-4 group (6 liver, 2 lung, 1 intraperitoneal and 1 brain). There was a

significant difference in the development of distant metastases between the two groups ($P = 0.014$). The overall median survival in the group of patients receiving neo-adjuvant treatment was 76 months (range 1.5–87 months). In the patient group that showed a downstaging towards a pT0-2 tumour after neo-adjuvant radiochemotherapy, the median survival was not reached during the observation period of 4.5 years. The median survival of the patients who showed minimal downstaging (pT3-4) was 76 months (3.5–79 months) and patients with tumour that were still irresectable had a median survival of 12 months (range 1.5–49 months). The survival difference between the pT0-2 and pT3–4 groups was almost significant ($P = 0.055$). A significant difference in survival was found between patients with a R0 and R1 (microscopic irradical) resection ($P = 0.0008$).

The 23 concomitant patients with primary resectable T1 and T2 rectal cancers treated with surgery only had a median observation time of 3.8 years (range 20–79 months). Local recurrence was found in 1 patient (4%). No distant metastases occurred. The median overall survival was not reached during this observation period. There was a significant difference ($P = 0.034$) in overall survival between the initially irresectable group ($n = 43$) and the primary resectable T1-2 group ($n = 23$) (Fig. 1).

## 4. Discussion

Among the 34 patients undergoing a resection subsequent to neo-adjuvant radiochemotherapy, only 4 were female. This can be explained by the fact that local recurrence often occurs in the anterior plane of the surgical margin. The female patients having three compartments in a relatively large and shallow pelvis, have an advantage when confronted by rectal cancer since fixation to the pelvic sidewalls is less frequent and adequate anterior extension of the resection can be achieved without compromising the bladder or the local radicality while performing a primary resection [7].

In this study, in patients with initially irresectable rectal tumours, neoadjuvant treatment with radio- and chemotherapy leads to a R0 resection in 74% of the patients. Moreover, when there is a downstaging after radiochemotherapy towards a postoperative stage of pT0-2 the survival (5 years overall survival of 90%) is comparable with that in the group of patients with primary resectable (T1-2) rectal tumours as shown in Fig. 2. These results are consistent with the literature [8–12]. The incidence of local recurrence in the downstaged group and primary resectable group was not significantly different. So, when an initially irresectable rectal tumour becomes downstaged to a resectable pT0-2 tumour, the final prognosis is the same as in a primary resectable T1-2 tumour. The patients who did not respond to the neo-adjuvant therapy had a significantly worse overall survival compared with responders ($P < 0.0001$).

There was a significant difference in the development of distant metastases between the 2 initially irresectable groups (pT0-2 vs. pT3-4, $P = 0.014$). Postoperative adjuvant therapy given in 17 patients did not correlate with the occurrence of distant metastases.

In this study, we showed an effect of neoadjuvant radiochemotherapy on initially irresectable rectal tumours. It is not clear to what extent preoperative chemotherapy plays an additional role in the phenomenon of downstaging and improvement in survival. Only a few randomised trials have investigated the role of preoperative radiochemotherapy compared with

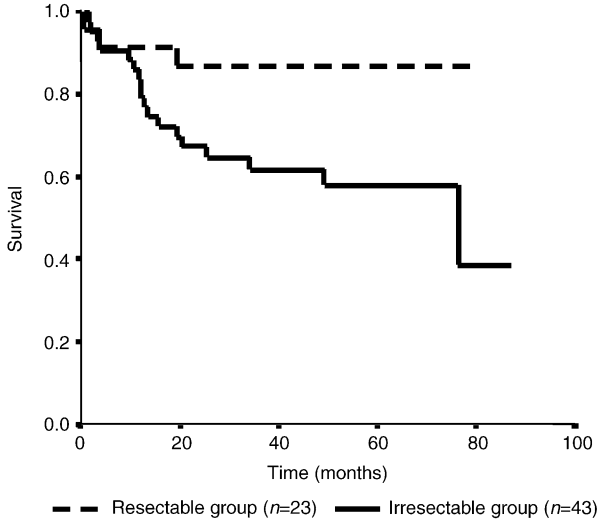


Fig. 1. Overall survival of the initially irresectable group and the primary resectable group with T1-2 tumours ($P = 0.034$).

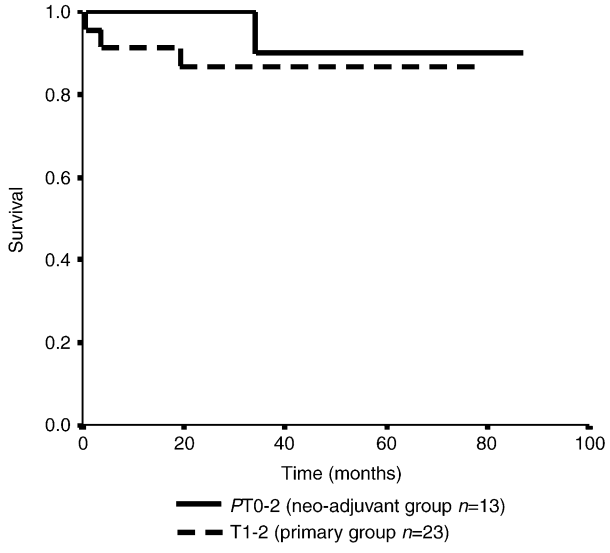


Fig. 2. Overall survival of the initially irresectable group postoperatively after maximal downstaging by chemoradiation (pT0-2) ($n = 13$) and the primary resectable group (T1-2) ($n = 23$) ($P = 0.58$).

radiotherapy alone in irresectable rectal cancers [13–15]. A slight prolongation of survival was found in one study [13]. These studies and several large phase II studies [16], show favourable results following combination treatments. However, until now, evidence for any benefit from neoadjuvant chemotherapy is limited due to the lack of randomised clinical trials investigating the role of neo-adjuvant chemotherapy in combination with radiotherapy for irresectable rectal cancers. Results of the ongoing Nordic trial should help to clarify this.

In our study, in 9 patients (21%) a resection of the tumour was not warranted after neoadjuvant radiochemotherapy because of fixation to the pelvic sidewalls, and these patients had a poorer prognosis.

To predict an insufficient response to neoadjuvant treatment, multiple potential predictive factors have been investigated in several studies, such as p53, BAX, p21, Bcl-2 and Ki-67 [17–20]. None of these factors show a sufficient specificity or sensitivity. Identification of a set of genes involved in the sensitivity for radiochemotherapy by the use of DNA microarray techniques might provide an answer in the future [21,22].

The addition of new drugs like oxaliplatin or irinotecan to existing 5-fluorouracil regimens in patients with advanced colorectal tumours improves response rates and the duration of response, and, possibly, overall survival [23–26]. These regimens might also increase the level of downstaging in advanced rectal cancers.

In conclusion, downstaging of irresectable rectal cancers results in acceptable local control rates, and a fair prognosis for survival. Optimisation of the neoadjuvant regime, using newly available drugs, might further improve these results.

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