Neoadjuvant Radiochemotherapy for Patients With Locally Advanced Rectal Cancer Leads to Impairment of the Anal Sphincter

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Neoadjuvant radiochemotherapy (RCTx) has become an acceptable therapy for patients with locally advanced rectal cancer. However, little is known about the effect of the RCTx on the function of the anal sphincter. Forty-one consecutive patients with locally advanced rectal cancer (cT3, N+) underwent neoadjuvant RCTx with subsequent resection. All patients were examined clinically and by anal manometry for their anal sphincter function. A multichannel water-perfused catheter system was used, and resting pressure, maximum squeeze pressure, and length of the anal high-pressure zone were determined prior to the neoadjuvant therapy and before the operation. The length of the high-pressure zone did not change after the neoadjuvant therapy. However, resting and maximum squeeze pressure decreased significantly after preoperative RCTx. This effect was more pronounced for the resting pressure rather than the maximum squeeze pressure, indicating that the internal sphincter is primarily affected. These results correlated with the clinical data showing an impaired continence status in patients treated with neoadjuvant therapy. Neoadjuvant RCTx leads to impairment of the anal sphincter predominantly in the internal sphincter. This effect may enhance the surgical impairment of continence after curative resection.
(J GASTROINTEST SURG 2006;10:309–314)

KEY WORDS: Anal sphincter, neoadjuvant therapy, anal manometry

Neoadjuvant radiochemotherapy has become an acceptable therapeutic tool for the treatment of locally advanced rectal cancer.[1–3] It may increase the rate of curative resection by downstaging[2,3] and may provide sphincter preservation in tumors located in the distal rectum.[4–6] Additionally, by applying irradiation preoperatively, oxygen tension in the tumor is higher due to untouched blood supply, leading to a more effective treatment.[7]

Several national randomized studies demonstrated a beneficial effect of neoadjuvant radiochemotherapy compared with adjuvant treatment or surgery alone. The Swedish Rectal Cancer Trial demonstrated an improved survival with a preoperative 5 × 5-Gy regimen compared with surgery alone.[8] The Dutch Colorectal Cancer Group showed better local tumor control with preoperative irradiation leading to a reduction in local recurrences.[9] The German Trial CAO/ARO/AIO-94[10] presented data from an interim-analysis including 805 patients randomly assigned to neoadjuvant radiochemotherapy or adjuvant radiochemotherapy, showing that preoperative radiochemotherapy does not bear a higher risk for complications in regard to postoperative morbidity compared with the adjuvant regimen and has a favorable impact on survival.

However, little is known about the effect of preoperative radiochemotherapy on the anal sphincter function. Most of the published studies addressing anal sphincter function were done after the resection of the rectum, making it impossible to distinguish between the solely effect of radiochemotherapy prior to the resection or the detrimental effect of surgery in addition to the neoadjuvant therapy.[11,12] It is well known that surgery alone, meaning low anterior resection, leads to a poor functional outcome; even so, anal sphincter function is normal in these studies.[13,14]

Knowledge of the potential detrimental effect of pelvic irradiation comes largely from studies in patients treated for prostate or bladder cancer.[15] Some studies suggest that anal sphincter impairment occurs often after irradiation, whereas others claim that the

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1091-255X/06/$—see front matter
doi:10.1016/j.gassur.2005.04.001

anal sphincter is unaffected.[16–20] Gervaz and colleagues[21] nicely showed that irradiation leads to a radiation-induced fibrosis based on an overproduction of fibrogenic cytokines, such as transforming growth factor-β1. This leads to the overproduction of collagen, fibronectin, and integrins. Histologically, endothelial damage, collagen deposition, and sclerosis can be observed.[22–24]

The effect of neoadjuvant radiochemotherapy on anal sphincter function in patients with rectal cancer is largely unknown. This effect might add to the poor functional outcome after low anterior resection.

PATIENTS AND METHODS

The study population consisted of 41 consecutive patients with locally advanced rectal cancer (uT3) considered for neoadjuvant radiochemotherapy followed by curative anterior or low anterior resection. Primary tumor staging was done with magnetic resonance imaging, abdominal ultrasonography, and endoscopy with ultrasound. All patients underwent clinical examination and manometry of the anal sphincter prior to the neoadjuvant radiochemotherapy and before the resection. Continence status was assessed by a modified Wexner score. The continence score postoperatively was measured 2–4 weeks after closure of the protective ileostomy.

Neoadjuvant Radiochemotherapy

Chemotherapy consisted of six cycles of 5-fluorouracil as continuous infusion in doses of 250 mg/m^2. Radiotherapy was administered with a total dose of 45 Gy in fractions at 1.5 Gy per day treated daily, 5 days a week. The irradiation is designed to include the entire tumor bed up to the internal iliac nodes.

Surgery

The operation was performed 4–6 weeks after the end of the neoadjuvant radiochemotherapy. Resection was done according to the principles of total mesorectal excision, meaning sharp dissection under direct vision along the parietal pelvic fascia, preserving the pelvic hypogastric nerve supply. Reconstruction was done by stapled end-to-end anastomosis with the level of the anastomosis reaching from 2 cm up to 8 cm from the anal verge depending on the location of the carcinoma. No pouch reconstruction or other type of new reservoir was created.

Manometry

Anorectal manometry was performed by using an eight-channel water-perfused catheter system. The catheter was connected to a polygraph and monitored and analyzed with Polygram for Windows, Version 2.0 (Synectics Medical, Medtronic, Middlesex, England). The patients were placed in a left lateral position. After insertion of the catheter within the rectum, a 3-minute adaptation period was allowed. Hereafter, the catheter was pulled back through the sphincter region in 1-cm increments to measure the length of the sphincter. Resting pressure was assessed by placing the manometry catheter within the high-pressure zone and leaving it there for 2 minutes. For evaluation of the maximum squeeze pressure, the catheter was placed within the high-pressure zone and the patients were asked to maximal squeeze. Attention was paid to the fact that only the sphincter muscles were used without squeezing the gluteal muscles. All measurements were done at least five times, and the mean was calculated. In 14 of 41 patients, manometry data were available after the resection and replacement of a potential protective stoma.

Statistical Analysis

For comparison of the manometry data, a two-tailed *t* test was used; for comparison of the continence score, a Mann-Whitney *U* test for nonparametric data was used. $P < 0.05$ was considered statistically significant.

RESULTS

There were 10 women and 31 men (median age, 61 years; age range, 34–81 years). All patients were diagnosed with locally advanced rectal cancer (uT3) and completed the entire neoadjuvant radiochemotherapy protocol. The control group consisted of 30 people not having any symptoms regarding anal sphincter problems. Anal manometry was performed prior to the radiation and chemotherapy and before the operation, meaning 4–6 weeks after the radiochemotherapy. Manometry results of the control group were not significantly different compared with the group of patients before the neoadjuvant radiochemotherapy (Fig. 1). As seen in Figures 1 and 2, the length of the anal sphincter did not decrease significantly after the radiochemotherapy, whereas resting pressure and maximum squeeze pressure decreased significantly after neoadjuvant radiochemotherapy. The resting pressure decreased by almost 21% compared with a 14% decrease for the maximum squeeze pressure, demonstrating a more pronounced effect of the radiochemotherapy on the internal anal sphincter. This decrease in sphincter pressure was even more pronounced after the operation and closing of the diverting stoma. These manometric