Effect of Preoperative Radiochemotherapy on Lymph Node Retrieval After Resection of Rectal Cancer

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Hypothesis: Preoperative radiochemotherapy for advanced rectal cancer results in fewer lymph nodes detected in the tumor-bearing specimen.

Design: Nonrandomized control trial with analysis of a prospective perioperative database.

Setting: Department of Surgery of a large-volume university hospital.


Interventions: During the study period 184 patients (81%, control group) underwent surgery without receiving preoperative radiochemotherapy. Forty-two patients (19%, study group) who had advanced rectal cancer (modified Dukes stages B [tumors that have penetrated the muscle layer of the bowel wall or have gone through the bowel] or C [tumors that have spread to the lymph nodes in the same region]) received preoperative radiochemotherapy (2 cycles of fluorouracil, 4500 rad) during this period. Most patients underwent anterior rectal resection in both groups (77.7% of those who did not receive preoperative radiochemotherapy and 71.8% of those who did), the remaining patients were treated with abdominoperineal resection.

Results: A mean (SEM) of 19 (1) lymph nodes per specimen were detected in the control patients, while significantly fewer lymph nodes were detected in study patients (13 [1]; P < .05). The rate of inadequate lymph node staging (pNx) increased from 7% in the control group to 12% in the study group (P = .06). Pathological lymph node staging disclosed that significantly more study patients who received preoperative radiochemotherapy had modified Dukes stage A (tumors that are found only in the inner wall or rectum) cancer when compared with the control group (17% vs 0%, respectively; P < .05).

Conclusions: Preoperative radiochemotherapy for advanced rectal cancer results in a significant decrease of lymph nodes detected within the tumor-bearing specimen. Preoperative radiochemotherapy induces significant downstaging with fewer positive lymph nodes and more patients presenting with Dukes stage A rectal cancer. Great care must be taken to remove an adequate number of lymph nodes and more sophisticated pathological techniques of lymph node detection are required since the tumors of ever-increasing numbers of patients are inadequately classified.

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IMPROVING long-term survival remains a major issue in the management of resectable rectal cancer. Colorectal cancer is a leading cause of morbidity and mortality with approximately 300,000 new cases and 200,000 deaths per year in the United States and in Europe. Because of the high risk of local recurrence or distant metastases after curative resection of rectal cancer, the 5-year survival rate may be as low as 50%. To improve these unfortunate survival rates after curative resection of rectal cancer, different protocols of preoperative radiochemotherapy have been proposed and evaluated. It seems as if preoperative radiochemotherapy induces tumor downstaging in 60% of all patients with increased curative resection rates, decreased frequency of local recurrence, and improved survival rates. Despite these promising results, to our knowledge, no information is available regarding the lymph node retrieval after preoperative radiochemotherapy and whether this therapeutic option influences postoperative pathological lymph node staging. These issues are of interest since the presence or absence of nodal metastases is the single most important prognostic factor in resectable colorectal cancer. Adequate tumor staging according to the standards of
SUBJECTS, MATERIALS, AND METHODS

Between January 1, 1996, and March 31, 2001, a total of 226 patients underwent conventional curative resection of rectal cancer in the Department of Surgery, Ludwig Maximilians University (Klinikum Grosshadern), Munich, Germany. The control group consists of 184 patients who underwent curative surgery of rectal cancer without receiving preoperative radiochemotherapy during the study period. The study group consists of 42 patients with locally advanced rectal cancer (T3/T4N0M0 or modified Dukes stage B [tumors that have penetrated the muscle layer of the bowel wall or have gone through the bowel]; nodal-positive disease or modified Dukes stage C [tumors that have spread to lymph nodes in the same region]) who underwent preoperative radiochemotherapy.

Preoperative radiochemotherapy was administered in patients with symptoms suggestive of locally advanced rectal cancer. Locally advanced rectal cancer was defined as tumor stage T3 or T4 without nodal involvement (modified Dukes stage B) and/or suspicious tumor draining lymph nodes (diameter ≥ 1 cm [modified Dukes stage C]). Diagnosis was based on the findings of endorectal ultrasonographic, computed tomographic, or magnetic resonance tomographic scans. Computed tomographic and magnetic resonance tomographic studies were performed following ultrasonographic suggestion of locally advanced disease. In cases of divergent findings, using different diagnostic tools, the most advanced tumor stage was considered for the therapeutic decision. In patients without ultrasonographic suggestion of advanced rectal cancer, additional magnetic resonance tomographic or computed tomographic studies of the rectum were usually not done. The rectal ultrasonography was performed by surgical residents under direct supervision of one attending surgeon.

Radiochemotherapy consisted of 2 cycles of intravenous fluorouracil (500 mg/m² per day for 5 days) and a total irradiation dose of 4500 rad (25 fractions, 180 rad per fraction) administered according to a modification of the National Cancer Institute protocol. Chemotherapy as well as radiotherapy were administered in various institutions that all agreed to apply the aforementioned modification of the National Cancer Institute protocol. Radiotherapy was administered using a rectum-pelvis-box that included the tumor site within the pelvis as well as the lymphatic draining area reaching up to the bifurcation of the common iliac artery (N1-N3 lymph nodes). Surgery was performed at 4 to 6 weeks after termination of preoperative radiochemotherapy in agreement with the findings of Francois et al. After wound healing, chemotherapy was completed with 4 additional cycles of intravenous fluorouracil (500 mg/m² per day for 5 days).

Four different surgical wards (A through D) contributed patients to the present study (Table 1). Within each ward 2 board-certified surgeons (C.M., G.M., and F.W.S.) performed surgery for rectal cancer. No significant variations regarding the number of patients contributed who did and did not receive preoperative radiochemotherapy were observed. All surgeons were trained under direct supervision and responsibility of the departmental chairperson (F.W.S., ward D). The surgical results of all contributing surgeons were controlled by departmental quality control.

Surgery consisted of abdominoperineal resection in 22.3% of all patients who did not receive preoperative radiochemotherapy and in 28.6% of all patients who received neoadjuvant therapy. All other patients underwent anterior resection (77.7% and 71.4%, respectively). Radical resection of the cancer-bearing specimen included the lymph nodes adjacent to the inferior mesenteric artery and total mesorectal excision as described by Carlsen et al. No differences were detected between the patients who received and those who did not receive preoperative radiochemotherapy regarding the surgical procedures performed for curative resection of rectal cancer. Since findings from a recent multicenter study indicated that minimal invasive surgery may also influence the number of lymph nodes resected with the cancer-bearing specimen, only patients who underwent conventional open surgery for rectal cancer were considered for this study. Patient information concerning perioperative and early postoperative data was prospectively collected in the departmental database to evaluate the influence of preoperative radiochemotherapy on postoperative lymph node retrieval within the tumor-bearing specimen. Tumor staging as reported herein is based on the results of pathological evaluation of the resected specimens. Preoperative staging is based on the findings of transrectal ultrasonographic, computed tomographic, and magnetic resonance tomographic scans.

Data were analyzed using 1-way analysis of variance (ANOVA) and Newman-Keuls, Dunn, and χ² tests. Differences were considered statistically significant at P<.05. Data are presented as mean (SEM).

RESULTS

CONTROL GROUP: PATIENTS WHO DID NOT RECEIVE PREOPERATIVE RADIOCHEMOTHERAPY

Between January 1, 1996, and March 31, 2001, a total of 184 patients underwent surgical treatment with curative intention for rectal cancer without prior administration of radiochemotherapy. Pathological evaluation revealed that no patients had Dukes stage A rectal cancer, while 61 patients had Dukes stage B rectal cancer, and 72 patients had Dukes stage C rectal cancer. Modified Dukes stage D (tu...
tumors that have spread to distant sites) rectal cancer was observed in 51 control patients during the study period (Figure). Within the resected specimens, 19.1 (0.8) lymph nodes were detected for pathological examination. A mean of 3.1 (0.4) of these lymph nodes disclosed cancer-positive results. Inadequate numbers of lymph nodes (pNx) were resected in 13 patients (7.1%).

**STUDY GROUP: PATIENTS WHO RECEIVED PREOPERATIVE RADIOCHEMOTHERAPY**

During the study period a total of 42 patients underwent preoperative radiochemotherapy for locally advanced rectal cancer prior to curative resection. Among these patients 7 had Dukes stage A rectal cancer (P < .05 vs control patients), 17 had Dukes stage B disease, and 11 had Dukes stage C disease. Seven patients were initially seen with Dukes stage D rectal cancer (Figure). Within the resected cancer-bearing specimen, 13.6 (0.9) lymph nodes underwent pathological evaluation (P < .05 vs control patients) and 1.4 (0.1) of these lymph nodes were cancer infiltrated (P < .05 vs control patients). Impossible lymph node staging (pNx) caused by inadequate numbers of recovered lymph nodes was observed in 11 patients of the study group (11.9%).

**RESECTED LYMPH NODES IN RELATION TO PRIMARY CANCER SIZE**

Fewer lymph nodes were resected in patients with preoperative radiochemotherapy with a cancer size pT3 when compared with patients who did not receive neoadjuvant therapy and who had equal cancer sizes (Table 2). In all other cancer sizes statistical significance was not reached.

**NUMBER OF LYMPH NODES IN RELATION TO SURGICAL PROCEDURE**

While no significant differences regarding the ratio of anterior and abdominoperineal resections were observed between both groups, we detected significant differences regarding the number of lymph nodes resected with the procedures. In patients who did not receive preoperative radiochemotherapy, anterior rectal resection resulted in 19.3 (0.6) lymph nodes per specimen, while specimens after abdominoperineal resection contained 16.1 (1.1) lymph nodes (P < .05). In patients who did receive preoperative radiochemotherapy, 14.0 (0.8) and 14.1 (2.0) lymph nodes per specimen, respectively, were detected (P < .05 vs corresponding control patients).

**TUMOR LOCATION, HEIGHT OF THE ANASTOMOSIS, AND LATERAL AND DISTAL MARGINS**

In control patients the tumor (8.4 [0.3] cm vs 6.2 [0.6] cm from the anal verge; P < .05) as well as the anastomosis (5.1 [0.3] cm vs 3.5 [0.3] cm from the anal verge; P < .05) were located significantly higher than in the patients who received preoperative radiochemotherapy. No differences between both patient groups were observed regarding the lateral (1.9 [0.1] vs 1.7 [0.3] cm, respectively) or the distal margins (2.9 [0.1] vs 2.8 [0.2] cm, respectively).

**COMMENT**

Improvement of disease-free and long-term survival after curative resection of rectal cancer remains the single most important issue of surgical oncology. Patients with locally advanced rectal cancer are known to be at increased risk of local recurrent disease with 5-year survival rates as low as 0% to 30%. Many patients present with locally advanced rectal cancer that might not be amenable to primary curative resection because of infiltration of surrounding organs or the pelvis. These patients may benefit from preoperative radiochemotherapy since it has been reported that downstaging of rectal cancer can be achieved in almost 60% of all patients undergoing preoperative radiochemotherapy. Preoperative radiochemotherapy may contribute to a better prognosis in patients with locally advanced rectal cancer since tumor-free resection margins have been reported after neoadjuvant therapy in more than 60% of patients with tumors that were not amenable to primary curative surgery.

Local recurrence rates, distant metastases as well as overall and disease-free survival are the most frequently addressed end points for the evaluation of different neoadjuvant radiochemotherapy regimens. During recent years, significant advantages have been reported regarding these oncological parameters in several studies on preoperative radiochemotherapy for advanced rectal cancer when compared with the surgical treatment alone.

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**Table 1. Number of Patients Contributed by Each Surgical Ward**

<table>
<thead>
<tr>
<th>Surgical Ward</th>
<th>Patients Who Did Not Receive Preoperative Radiochemotherapy, No. (%) (n = 184)</th>
<th>Patients Who Received Preoperative Radiochemotherapy, No. (%) (n = 42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>20 (10.9)</td>
<td>4 (9.5)</td>
</tr>
<tr>
<td>B</td>
<td>69 (37.5)</td>
<td>14 (33.3)</td>
</tr>
<tr>
<td>C</td>
<td>43 (23.4)</td>
<td>14 (33.3)</td>
</tr>
<tr>
<td>D</td>
<td>52 (28.3)</td>
<td>10 (23.8)</td>
</tr>
</tbody>
</table>

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pared with surgery alone or with the administration of postoperative radiochemotherapy.\textsuperscript{1,4,14,15} Nevertheless, Pålhlman and Grimelius\textsuperscript{14} also reported increased rates of wound infections after preoperative radiotherapy leading to a prolonged postoperative hospital stay. These patients, however, underwent surgery within 1 week after termination of radiotherapy, which may have contributed to the increased rates of postoperative wound infections.

After preoperative radiochemotherapy was introduced for advanced rectal cancer, to our knowledge, no study has focused on the number of lymph nodes retrieved within the cancer-bearing specimen after preoperative radiochemotherapy, although it has been reported that radiotherapy induces a significant shrinking of lymph node size.\textsuperscript{16} Furthermore, it is not known whether this novel therapeutic option has detrimental effects on postoperative pathological lymph node staging. These questions seem to be of special interest since the presence or absence of nodal metastases has been reported to be the single most important prognostic factor in resectable colorectal cancer.\textsuperscript{7} To address these issues a large prospective perioperative and follow-up database of a single institution was analyzed regarding the number of lymph nodes resected from those who received and did not receive preoperative radiochemotherapy for rectal cancer.

Data reported herein show that preoperative radiochemotherapy in advanced rectal cancer induces a significant decrease of lymph nodes being detected within the tumor-bearing specimen. Furthermore, significantly fewer tumor-infiltrated lymph nodes are detected in patients who received preoperative radiochemotherapy. The decreased number of tumor-positive lymph nodes correlates with the significant increase of less advanced pathological cancer stages in patients who received preoperative therapy. These observations are of special interest since radiochemotherapy was administered only to patients who had a preoperative diagnosis of advanced rectal cancer (modified Dukes stages B or C) and, therefore, indicate the downstaging effects of this therapeutic approach.

The results of preoperative staging procedures with transrectal ultrasonography, computed tomography, and magnetic resonance tomography are under investigation and no clear recommendation regarding optimal pretherapeutic staging is available.\textsuperscript{17} The remaining uncertainty regarding the exact preoperative tumor stages is of importance since preoperative radiotherapy is known to result in significant tissue alterations and shrinking of lymph nodes that does not allow for an exact postoperative validation of the preoperative findings regarding cancer stage.\textsuperscript{16}

The proportion of patients having modified Dukes stage D rectal cancer (28\%) within the control group is high, nevertheless, only patients after curative resection of rectal cancer qualified for the departmental follow-up database. Patients with modified Dukes stage D rectal cancer, therefore, underwent curative resection of the cancer and the metastasis within one or multiple surgical interventions.

The observed decreased number of lymph nodes within the resected specimens may not only be because of the effects of preoperative radiochemotherapy. Concurrent with the introduction of preoperative radiochemotherapy for advanced rectal cancer the use of laparoscopic surgery has gained more attention in our institution as well as in other surgical centers.\textsuperscript{18-20} A recent multicenter trial reported that this novel surgical technique resulted in a mean number of 12.1 lymph nodes within the resected specimens.\textsuperscript{9} We, therefore, decided to consider only patients after conventional open surgery for the present study to exclude this possible influencing factor for postoperative lymph node retrieval.

The observation of a significantly lower tumor as well as anastomosis height in patients who received neoadjuvant therapy is of interest since it may be a consequence of scar tissue formation and tissue shrinkage after preoperative radiochemotherapy. This observation does not explain the reported occurrence of significantly fewer lymph nodes within the resected specimens of these patients since identical surgical techniques were applied in all patients with rectal cancer.

The assessment of the number of lymph nodes within the resected specimen in relation to the size of the primary cancer revealed that only in patients with a primary cancer size of pT3 significantly more lymph nodes were resected from those who did not receive preoperative radiochemotherapy, while the differences observed in patients with primary cancer sizes pT0, pT1, and pT4 did not reach statistical significance. These findings indicate that the number of lymph nodes did not directly relate to the primary cancer size and that possible variations in the distribution of cancer sizes did not account for the significant differences regarding lymph node size.

Table 2. Number of Lymph Nodes in Relation to Primary Cancer Size

<table>
<thead>
<tr>
<th>Primary Cancer Size (Pathological Finding)</th>
<th>Patients Who Did Not Receive Preoperative Radiochemotherapy</th>
<th>Patients Who Received Preoperative Radiochemotherapy</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Lymph Nodes</td>
<td>No. of Patients</td>
<td>No. of Lymph Nodes</td>
</tr>
<tr>
<td>T0</td>
<td>8.0 (2.0)</td>
<td>3</td>
<td>12.0 (2.3)</td>
</tr>
<tr>
<td>T1</td>
<td>21.0 (0.9)</td>
<td>2</td>
<td>11.0 (1.1)</td>
</tr>
<tr>
<td>T2</td>
<td>16.8 (1.7)</td>
<td>15</td>
<td>12.9 (1.1)</td>
</tr>
<tr>
<td>T3</td>
<td>18.7 (0.6)</td>
<td>129</td>
<td>15.2 (1.1)</td>
</tr>
<tr>
<td>T4</td>
<td>22.8 (3.7)</td>
<td>32</td>
<td>11.4 (4.5)</td>
</tr>
</tbody>
</table>

*Data are given as the mean (SEM). Ellipses indicate not applicable.
†By TMN staging T is used to describe the size and extent of the tumor. The higher the number the deeper the penetration through the bowel wall. Tx indicates undetermined.
retrieval from those who did and did not receive preoperative radiochemotherapy for rectal cancer.

Another interesting observation of our study is the significant difference regarding lymph node retrieval between specimens after anterior rectal resection vs abdominoperineal resection only in patients who did not receive preoperative radiochemotherapy (19 [1] vs 16 [1]; P<.05). In patients who received neoadjuvant therapy, no significant differences were observed. The number of resected lymph nodes was, however, significantly lower than in control patients who underwent anterior rectal resection (14 [1]; P<.05) or abdominoperineal resection (14 [2]; P<.05). The clinical and oncological implications of these observations remain unclear and require further investigation.

Since it has been reported that significant shrinking of the lymph node size may occur after radiochemotherapy,16 it appears that pathological workup of the resected specimens is an important issue raised by our findings. In general, the specimens of our patients who did and did not receive preoperative radiochemotherapy were not processed by attending pathologists but by technicians and trainees. Furthermore, alcohol degreasing was not done in these specimens. It, therefore, appears that the search for lymph nodes must be standardized and requires alcohol degreasing in cancer specimens taken from patients who received preoperative radiochemotherapy. This procedure, however, is not applied in most departments. Therefore, to avoid incomplete staging of patients who received preoperative radiochemotherapy, it is necessary to standardize pathological techniques of lymph node retrieval and specimen preparation. Our findings lead us to propose that the introduction of sophisticated preoperative treatment regimens (radiochemotherapy) for locally advanced rectal cancer also warrants the use of more advanced methods of lymph node detection in the cancer specimen, that is, standard alcohol degreasing.

The findings of our study are relevant since the conditions of ever-increasing numbers of patients are inadequately classified, leading to an unclear prognosis for the individual patient and difficulties with comparing different therapeutic regimens for advanced rectal cancer. Data reported herein warrant further evaluation in larger study groups, possibly multicenter trials.

Provided that our findings are confirmed despite the suggested changes of pathological technique (ie, alcohol degreasing) the current tumor classification according to the UICC should be revised regarding the number of lymph nodes necessary for correct classification after preoperative radiochemotherapy.

This single-center study indicates that preoperative radiochemotherapy results in a significantly decreased number of lymph nodes being resected with the cancer-bearing specimen. Preoperative radiochemotherapy, furthermore, induces a significant decrease of the number of tumor-infiltrated lymph nodes and significantly more patients are postoperatively diagnosed as having less advanced cancer stages (modified Dukes stage A). These findings are a strong indicator for the downstaging effects of preoperative radiochemotherapy, since this therapy was only adminis-

tered to patients who had a preoperative diagnosis of advanced stages (modified Dukes stages B or C) of rectal cancer. Our findings, therefore, support the beneficial oncological results of preoperative radiochemotherapy reported by other groups13-15 as we can clearly show a reduction of tumor-positive lymph nodes. The observation of a general reduction of lymph nodes retrieved within the cancer-bearing specimen, however, warrants further evaluation since correct postoperative staging of the patients who received preoperative radiochemotherapy is endangered.

Preliminary data of this work were presented at the Ninth International Congress of the European Association for Endoscopic Surgery, Maastricht, the Netherlands, June 16, 2001; and at the 42nd Meeting of the Austrian Surgical Society, Graz, June 16, 2001.

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REFERENCES