Preliminary Results of Pelvic Autonomic Nerve-preserving Surgery Combined with Intraoperative and Postoperative Radiation Therapy for Patients with Low Rectal Cancer

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Background: In Japan, lateral lymphadenectomy was widely performed for patients with stage II–III rectal tumors because it was thought to contribute to good local control, but the pelvic autonomic nerves were thus sacrificed. Although autonomic nerve-sparing surgery with lateral lymph node dissection has been tried from around 1987, the type of nerve sparing varied and the indications were not established. To examine the possibility of expanding the indications for total pelvic autonomic nerve preservation for patients with low rectal cancer, we conducted a pilot study.

Methods: Between 1993 and 1997, a total of 50 patients with low rectal cancer underwent pelvic autonomic nerve preservation with lateral lymphadenectomy of both sides and intraoperative radiation therapy followed by postoperative radiation therapy.

Results: The median follow-up period for surviving patients was 41 months. The 3-year local control rates for all patients, with stage I–II and stage III tumors were 88% (95% confidence interval, 78–97%), 97% (90–100%) and 73% (52–94%), respectively. The site of local recurrences was not near or within the preserved plexus.

Conclusions: The preliminary results showed good local control rate for patients with stage I–II tumors. For patients with stage III tumors, the local control rate was unsatisfactory, but nerve sparing was not the cause of local recurrence. Further investigation of function-preserving surgery without decreasing curability is needed.

Key words: low rectal cancer–pelvic autonomic nerve-preserving surgery–intraoperative and postoperative radiotherapy

INTRODUCTION

In patients with advanced rectal cancer, it is difficult to preserve urinary and sexual function with the conventional surgical procedures which resect the mesorectum bluntly and blindly. In addition, the reported local recurrence rate is rather poor, 20–30% (1–5). More recently, the local recurrence rate has declined to 5–8% owing to the introduction of the total mesorectal excision (TME) technique with/without adjuvant therapy (2,6,7). In Japan, lateral lymph node dissection was thought to be necessary to obtain good local control and pelvic autonomic nerves were sacrificed for patients with advanced-stage rectal cancer (8). Pelvic autonomic nerve preservation (PANP) surgery with lateral lymph node dissection has been tried from around 1987; the type of PANP varied and the indications were not established. In 1993, it was not commonly accepted to perform total PANP for patients who had a potential for stage II or III rectal cancer. We therefore started this study to examine the possibility of expanding the indications for total PANP. We report here the preliminary results.

MATERIALS AND METHODS

PATIENT POPULATION AND TUMOR CHARACTERISTICS

Between 1993 and 1997, 50 patients with low rectal cancer, at or below the peritoneal reflection, were enrolled in this pilot study. The patient selection criteria were (1) biopsy-proven low rectal cancer, (2) a tumor without direct invasion to bilateral pelvic nerve plexuses on preoperative evaluation and at surgery, (3) a tumor without bilateral lateral lymph node involvement con-
firmed histologically at surgery, (4) without distant metastasis (except for liver metastasis for which complete resection is possible) and (5) written informed consent. During this period, 66 patients were considered eligible preoperatively, but 16 patients were revealed to be ineligible at surgery and excluded from the study. The pretreatment evaluation included a complete history, physical examination, colonoscopy, complete blood count, liver function profile, creatinine, serum carcinoembryonic antigen (CEA), chest X-ray, ultrasound of the liver, computed tomography (CT) scan of the abdomen and the pelvis, magnetic resonance imaging (MRI) of the pelvis and endorectal ultrasound. The patient and tumor characteristics are given in Table 1.

SURGERY

The operative procedures included low anterior resection in 26 patients and abdominoperineal resection in 24 and both were performed with combining the TME technique and lateral lymph node dissection. All patients underwent total PANP, i.e. the hypogastric nerve and bilateral pelvic nerve plexuses were preserved, with lateral lymphadenectomy on both sides.

Table 1. Patient and tumor characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No.</th>
<th>Age (median)</th>
<th>Gender</th>
<th>Type of surgery*</th>
<th>Tumor classification</th>
<th>Pathological stage</th>
<th>Histologic grade</th>
<th>Perineural invasion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>40–73 (57) years</td>
<td>Male</td>
<td>APR</td>
<td>T1</td>
<td>I</td>
<td>Well differentiated</td>
<td>Present</td>
</tr>
<tr>
<td></td>
<td></td>
<td>34</td>
<td>Female</td>
<td>LAR</td>
<td>T2</td>
<td>II</td>
<td>Moderately differentiated</td>
<td>Absent</td>
</tr>
<tr>
<td></td>
<td></td>
<td>16</td>
<td></td>
<td>T1</td>
<td>T3</td>
<td>III</td>
<td>Poorly differentiated</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LAR</td>
<td>T4</td>
<td>IV</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>

*R APR, abdominoperineal resection; LAR, low anterior resection.

RADIATION THERAPY

The purpose of radiation therapy in this study was for prophylactic treatment only to the tissue near and within the preserved pelvic nerve plexuses which were not dissected and might have microscopic residual tumor. This was different from common postoperative radiation therapy (PORT) for tumor bed and regional lymph nodes. The purpose of combination of intraoperative radiation therapy (IORT) with PORT is to reduce the radiation dose to the small intestine while maintaining the intensity of radiation at the target. This leads to a decrease in the rate of late radiation toxicities, such as diarrhea and intestinal obstruction, which is a major problem in performing common PORT using external beam radiotherapy alone. The small intestine does not receive any radiation using IORT.

INTRAOPERATIVE RADIATION THERAPY

All patients received IORT to the bilateral preserved pelvic nerve plexuses separately. The size of the cone used was 4 cm in diameter and the electron energy used was 5 MeV. The radiation doses delivered were 15 Gy. The clinical target volume (CTV) included the pelvic nerve plexuses excluding the ureters and the planning target volume (PTV) was determined by fitting the cone to the plexuses in the operating room under direct vision by the surgeons and radiation oncologists (Figs 1 and 2).

POSTOPERATIVE RADIATION THERAPY

We started PORT 18–50 days (median 27 days) after surgery. The planned radiation dose was 30 Gy, 15 fractions of 2 Gy given as one fraction per day and 5 days per week with 21 MV photons. The irradiation techniques used were a four-field approach (AP-PA and R–L lateral) and 25% weight for each beam at the isocenter. The CTV included the preserved pelvic nerve plexuses, whereas the PTV was determined anatomically. The AP-PA fields extended 1 cm lateral to the widest bony margin of the true pelvis. The superior border of the fields was at the sacral
promontory and the inferior border was at the lower edge of the coccyx regardless of the type of surgery. The lateral fields had the same superior and inferior extent as the AP-PA fields. The posterior border was located at the posterior border of the sacrum. The anterior border was generally 1–2 cm anterior to the sacral promontory. All but four patients received PORT. Two of the 46 patients who received PORT could not complete the planned treatment (a total dose of 2 and 16 Gy) owing to fistula and abscess, respectively, and one patient received 46 Gy because of the existence of microscopic residual tumor.

**EVALUATION OF URINARY AND SEXUAL FUNCTION**

We evaluated urinary and sexual function using questionnaires 3, 6, 12 and 24 months after surgery. All but one patient were evaluable for urinary function and 15 of 34 male patients were evaluable for sexual function.

**FOLLOW-UP**

The patients were observed for local failure and distant metastasis every 3 months for the first 3 years, every 6 months for the next 2 years and once a year thereafter. At each visit, a history was taken, a physical examination was performed and the serum CEA level was determined. A CT scan of the abdomen and the pelvis, a chest X-ray and ultrasonography for detecting liver metastasis were performed every 3-6 months; colonoscopy was performed once a year. A CT scan of the chest was performed when appropriate. The median follow-up period for surviving patients was 41 months (range 18–69 months).

**STATISTICAL ANALYSIS**

All 50 patients were included in the analysis. The local control rate, progression-free survival and overall survival were calculated from the day of surgery using the Kaplan–Meier method (9). The differences between groups were estimated by the log-rank test (10). When a patient died without local recurrence, he was removed from the local control rate analysis. For the progression-free survival and overall survival analysis, any cause of death was also included. One patient, who was lost to follow-up with pulmonary metastases, was dealt with as dead at the time of last follow-up.

**RESULTS**

**PATTERNS OF FAILURE**

The incidence and pattern of failure were evaluated. The site of local recurrence was evaluated by pelvic CT scan. Eleven patients had died and 39 patients were alive as of the date of this report. Local recurrence was observed in six patients (Table 2). Four of these six patients completed the planned treatment; one patient did not undergo PORT because of delayed wound healing due to diabetes mellitus and one discontinued the PORT treatment owing to wound infection at 16 Gy. All local recurrences were found outside the IORT field and were not near or within the preserved pelvic nerve plexuses. In addition, all four patients were found to have perineural invasion.

Distant metastasis was observed in 13 patients. In two of them, local recurrence occurred concomitantly and in two patients local recurrence developed prior to distant metastasis. The first site of distant metastasis was the liver in eight patients, the lung in three, the bone in one and the skin in one.

**SURVIVAL AND TOXICITIES**

The 3-year overall survival, progression-free survival and local control rate were 78% (95% confidence interval, 66–91%), 70% (95% confidence interval, 57–83%) and 88% (95% confidence interval, 78–97%), respectively (Fig. 3). The 3-year local control rate for patients with pathological stage I (same as Dukes A), stage II (same as Dukes B) and stage III (same as Dukes C) disease were 92% (95% confidence interval, 76–100%), 100% and 73% (95% confidence interval, 52–94%), respectively. There was a significant difference in local control rate between the stage I–II and stage III patients ($P = 0.018$).

Forty of 49 evaluable patients had no urinary disturbance and nine had slight to moderate occasional incontinence, dull uresiesiethesia or sense of residual urine. Fourteen of 15 evaluable male patients could achieve intercourse preoperatively and 11 postoperatively.

**Table 2. Cases with local recurrences**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Pathological stage</th>
<th>Type of surgery</th>
<th>PORT (Gy)</th>
<th>Perineural invasion</th>
<th>Site of recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I</td>
<td>APR</td>
<td>30</td>
<td>Present</td>
<td>Presacral region</td>
</tr>
<tr>
<td>2</td>
<td>III</td>
<td>APR</td>
<td>0</td>
<td>Present</td>
<td>Presacral region and perineal skin</td>
</tr>
<tr>
<td>3</td>
<td>III</td>
<td>LAR</td>
<td>16</td>
<td>Present</td>
<td>Peritoneum</td>
</tr>
<tr>
<td>4</td>
<td>III</td>
<td>LAR</td>
<td>30</td>
<td>Present</td>
<td>Anastomosis</td>
</tr>
<tr>
<td>5</td>
<td>III</td>
<td>LAR</td>
<td>30</td>
<td>Absent</td>
<td>Bottom of pelvis</td>
</tr>
<tr>
<td>6</td>
<td>III</td>
<td>APR</td>
<td>30</td>
<td>Unknown</td>
<td>Bottom of pelvis</td>
</tr>
</tbody>
</table>

*Postoperative radiation therapy.
Although there are several reports concerning metastasis preoperatively, we could adopt PANP for patients with patients. If we could predict the actual existence of lymph node metastasis in the pelvis. Assuming that lateral lymphadenectomy is not performed for patients with pathological stage III tumors, the risk of residual positive lymph node metastasis is estimated to be from 17.5 to 36% (8,12–14). There is considerable controversy regarding the use of lateral lymphadenectomy with respect to local control, autonomic function, operative morbidity, etc. (15–18). In Western countries, lateral lymphadenectomy has rarely been performed to preserve autonomic nerves and adjuvant treatment is thought to be the most likely way to improve the surgical results. However, adjuvant treatment should not be performed simply to compensate for an inadequate conventional surgical procedure resecting the mesorectum bluntly and blindly (19). The role of adjuvant treatment for patients who undergo surgery with methods such as TME is now being investigated but has not yet been clarified. Moriya et al. (8) reported a low local recurrence rate (12%) with surgery alone including lateral lymphadenectomy, which is within the range of the reported series (10–15%) with adjuvant treatment (4,5,8). However, the routine use of lateral lymphadenectomy sacrificing the pelvic nerve plexus on both sides leads to serious urinary and sexual dysfunction for more than two-thirds of rectal cancer patients. If we could predict the actual existence of lymph node metastasis preoperatively, we could adopt PANP for patients with clinical stage II tumors and even for patients with clinical stage III tumors. Although there are several reports concerning preoperative staging using endorectal ultrasonography, pelvic CT scan and MRI (20–23), the accuracy remains at most 80%. We cannot know exactly whether the tumor is stage III or not even at surgery. We thought that total PANP with lateral lymph node dissection could be performed even for patients with possible stage III tumors, if lateral lymph node was not involved. We therefore examined the existence of lateral lymph node metastasis histologically at surgery by performing lateral lymphadenectomy except for the lymph nodes within or near the plexuses and then performed total PANP for the patients without lateral lymph node metastasis. According to this procedure, there may be microscopic residual tumor within or near the preserved plexuses. We therefore added IORT plus PORT to the preserved plexuses as adjuvant therapy to eradicate the possible residual tumor.

The radiation doses used were 15 Gy intraoperatively and 30 Gy postoperatively. We compared this treatment regimen with conventional treatment, i.e. 25 fractions of 2 Gy given as one fraction per day, 5 days per week, using the biologically effective dose (BED) (24). The calculated BEDs for this treatment and conventional treatment are 73.5 Gy10 and 60 Gy10, respectively. When corrected for time assuming that the PORT starts within 1 month from the day of surgery, these values are 52.7 Gy10 or more and 45.2 Gy10, respectively. This suggests that the dose of the present regimen is sufficient in the prophylactic setting, if the residual tumor is included in the CTV of IORT. In addition, this regimen appears to be feasible and the possibility of severe radiation-induced neuropathy seems to be rare, according to the results of several reported series (25–27).

We evaluated urinary and sexual function using questionnaires. However, the results are too early to report finally because of the relatively short follow-up period, except for the fact that none of the patients need the aid of a catheter. We shall report these results later with sufficient follow-up.

We observed the 3-year local recurrence rates of 0% and 27% for patients with stage II and III tumors, respectively. This means that our methods were fruitful for patients with stage II tumors, but unsatisfactory for stage III tumors. The site of local recurrence was outside the IORT field and was not within or near the preserved pelvic nerve plexus; the cause could be microscopic residual tumor after lateral lymphadenectomy or implantation at surgery. Perineural invasion of the tumor, which is one of the predictors of local recurrence (28,29), may partly explain the reason. In the present study, four of six patients with local recurrence were found to have perineural invasion histologically and one was not assessed. These findings suggest that preserving the pelvic nerve plexus does not influence the local control rate even for patients with stage III tumors. However, to improve local control, other methods of radiation delivery, such as PORT with chemotherapy, should be considered for patients with stage III tumors.

In conclusion, the pelvic autonomic nerve plexus can be totally preserved even for patients with stage III tumors without lateral lymph node metastasis. Further investigation concerning pelvic autonomic nerve function-preserving surgery without decreased curability according to individual tumor spread is needed.
References


