INTRODUCTION

The Japanese Society for Cancer of the Colon and Rectum recommends total mesorectal excision (TME) combined with radical extended retroperitoneal and lateral pelvic lymphadenectomy (RLPL) for the treatment of patients with T3/T4 extraperitoneal rectal adenocarcinomas without distant metastasis [1]. Western guidelines recommend TME [2] combined with chemoradiotherapy in patients without distant metastasis of T3/T4 tumors or mesorectal lymph node metastasis [3]. The best treatment results obtained in Western practice for patients with T3/T4 rectal adenocarcinomas with preoperative chemoradiotherapy followed by TME were associated with a 5-year pelvic recurrence of 6.0% and survival of 76.0% [4]. Treatment of this condition in Japan using TME plus RLPL resulted in a 5-year pelvic recurrence rate of 8.3% and survival of 77.0% [5]. Thus, both treatment options for rectal adenocarcinoma have similar results.

Classifications for rectal cancer staging differ in Japan and Western countries [1,7]. The main difference is that metastases to retroperitoneal or lateral pelvic lymph nodes (RLPNs) are considered regional node involvement in Japan, and patients are classified as stage III [1]. In Western practice, cancer dissemination through RLPNs is considered distant metastasis, and these patients are classified as stage IV, considered to have systemic tumor dissemination, and are not included in data related to curative intent [7]. Because stage classifications differ, comparisons of Western and Japanese rectal cancer treatment results are challenging.

The inclusion of stage III low rectal cancer patients with metastasis to RLPNs for treatment with curative intent should be a disadvantage for Japanese data. These patients have worse survival (5-year survival of 39.8%) and a greater pelvic recurrence rate (26.1%) than patients without RLPN metastases [5]. Therefore, similar treatment results of low rectal cancer obtained for both Western and Japanese treatments should indicate greater success for the Japanese protocol. This fact encourages Western researchers to consider treating rectal adenocarcinoma patients with TME plus RLPL. In fact, RLPL was initially performed in Western practice but was abandoned primarily because of its high morbidity [5]. Japanese surgeons refined RLPL with pelvic autonomic nerve preservation, which decreased surgical time, blood loss, and genitourinary dysfunction [5].

This study presents the follow-up data for morbidity, recurrence, and survival rates of a cohort of patients with low rectal adenocarcinoma that was included in a previous trial [8]. All patients were treated with TME plus RLPL, and patients with T3/T4 tumors or metastases to mesorectal lymph nodes or RLPNs underwent additional chemoradiotherapy.

Conflicts of interest: None.

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Local and national ethics committees approved this trial, and written informed consent was obtained from all patients. Between January 2004 and January 2007, 102 patients with rectal adenocarcinoma located at or below the peritoneal reflection, with TNM stage II and III established in preoperative exams, were enrolled in a previous prospective study [8,9]. Patients who agreed to participate in the study were enrolled, without selection of patients who might be suitable for TME plus RLPL. The aim of the previous study was to evaluate the accuracy of lymphoscintigraphy with technetium-99 m-phosphate and patent blue in the detection of metastases in RLPNs [8,9], which created a cohort of patients subjected to TME plus RLPL that was followed to evaluate surgical and oncological outcomes.

All patients underwent TME plus RLPL with pelvic autonomic nerve preservation performed by the same surgeon (the first author). Patients with abdominal and pelvic computed tomographic scans suggesting cT3/cT4 tumors or mesorectal or pelvic metastatic lymph nodes were subjected to preoperative chemoradiotherapy. This neoadjuvant treatment consisted of a 5,040-cGy dose of radiotherapy delivered in 180-cGy fractions per day, combined with a chemotherapy regimen of daily 5-fluorouracil (375 mg/m² of body surface) and leucovorin (30 mg/m² of body surface) delivered in a 5-day cycle, one during the first week and the other during the third week of radiotherapy. Patients with pT3/pT4 tumors or nodal metastases who did not receive neoadjuvant treatment underwent postoperative chemoradiotherapy following the same protocol. Four additional cycles of chemotherapy were given, one per month, either after surgery in patients subjected to preoperative chemoradiotherapy or after postoperative chemoradiotherapy, using the above-mentioned protocol of 5-fluorouracil and leucovorin. Patients with metastases to RLPNs, even with pt2 tumors or without metastases to mesorectal lymph nodes, were treated with adjuvant postoperative chemoradiotherapy.

TME included the ligation of the inferior mesenteric artery at the aorta. RLPL was performed according to the Japanese Society for Cancer of the Colon and Rectum protocol [1]. RLPL consisted of resection of para-aortic lymph nodes inferior to the left renal vein, lymphatic chains on both sides at the common iliac arteries, lymph nodes between the internal iliac arteries and veins, and between the internal and external iliac arteries and bilateral obturator lymph nodes. The pelvic autonomic nerve preservation consisted of preserving the hypogastric nerve and lateral pelvic branches.

All patients had low rectal tumors located at or below the peritoneal reflection. The extraperitoneal rectum was divided into three anatomic regions [8]. The upper rectum was considered the proximal 1/3 starting at the peritoneal reflection. The lower rectum was considered the lower 1/3 including the anal canal. The middle rectum was taken as the intermediate 1/3 rectal segment between the upper and lower rectum.

Operative mortality was defined as any patient death occurring within 30 days after surgery and at 30 days during the same hospitalization as the surgery [10]. Surgical morbidity was defined as any complication related to the surgical procedure and was divided into early (within 30 days of surgery) and late (after 30 days) postoperative morbidity. Late postoperative morbidity was identified as periods greater than 30 days after surgery and was evaluated until the end of the patient’s follow-up. Patients considered without postoperative morbidity did not have complications during their entire follow-up period.

For surgical morbidity analysis, only patients who underwent anastomosis were included in the fistula rate, only patients who underwent colorectal anastomosis were included in the fecal incontinency rate, and only male patients were included in the impotence rate. Patients who underwent total pelvic exenteration were excluded from genitourinary dysfunction rates, as these morbidities were expected. Severe bleeding was considered in patients if bleeding caused hypovolemic shock. In terms of colostomy prolapse, only patients who had a persistent problem that required surgical treatment were included.

A cohort of 102 patients was selected and followed to evaluate operative mortality and early and late morbidity. Pelvic cancer recurrence, distant metastasis occurrence, and survival were evaluated in 100 patients. Two patients were excluded from this analysis because histopathological analysis of surgical specimens identified a peritoneal implant in one patient and an in situ adenocarcinoma in a villous adenoma tumor in the other. Rectal cancer staging was performed using the 6th edition of the UICC/AJCC Cancer Manual [7]. Only surgical specimens obtained with TME were used for staging. Metastases to lymph nodes dissected by RLPL were described separately because the UICC/AJCC classification considers such metastases stage IV disease [7], whereas in the Japanese classification, they are N3, stage III [11].

The semi-parametric Kaplan–Meier’s method was used in the statistical analysis to evaluate survival. Survival curves were compared using the log-rank test. The cumulative hazards were estimated using the Nelson–Aalen estimator. The median follow-up period was calculated with the reverse Kaplan–Meier’s method, used to obtain the estimated period of potential follow-up. The analysis was performed in R (version 2.13) for Ubuntu version 11.10 Oneiric Ocelot.

Among the 102 patients with low rectal adenocarcinoma who underwent TME plus RLPL with pelvic autonomic nerve preservation, females were predominant, comprising 59.8% of the study group. Mean patient age was 56 years, with a median of 56.5 years, ranging from 22 to 90 years. The median level of serum albumin was 3.3 g/dl. Hypertension was present in 31.4% of the patients, diabetes in 12.7% of patients, and coronary artery disease with previous acute myocardial infarction in 3.9% of patients. Illiteracy was present in 32.2% of patients and defined as patients not having attended any school and not being able to read or write; 25.5% of patients did not finish elementary school.

Lower rectal tumors represented 49.1% of patients, middle rectal 37.2%, and upper rectal 13.7%. In terms of surgical procedures associated with RLPL, 40 patients underwent anterior rectal resections, 37 patients underwent abdominoperineal rectal resections, 14 patients underwent abdominoperineal rectal resections with partial colpectomy; six patients underwent anterior rectal resections with hysterectomy, three patients underwent total pelvic exenterations, and two patients underwent anterior rectal resections with partial cystectomy. Diversion colostomy of a colorectal anastomosis was performed in 46 anterior rectal resections, terminal Hartman’s colostomy was performed in two patients ineligible for anastomosis, and definitive colostomy was performed in 54 patients.

Surgical mortality was 3.9%. Two patients died of sepsis related to anastomotic leak, one patient died from respiratory sepsis, and one patient died from necrotizing fasciitis. Overall surgical morbidity was 33.3%. Events related to early postoperative morbidity are shown in Table I. Blood transfusion was necessary in 25 patients (24.5%), with a mean volume of 900 ml per patient. Mean operative stay was 8.8 days. Mean operative time was 187.9 minutes. Stay in the intensive care unit (ICU) was needed for 39 (38.2%) of the 102 patients, most of whom had surgical morbidities, with a mean stay of 6.7 days. The percentage of patients with late postoperative morbidity was 25.8% as shown in Table II.

Cancer treatment outcome was evaluated in 100 patients, with a median follow-up period of 41 months and mean follow-up of
76.3 months. In terms of adjuvant treatment, chemoradiotherapy was administered in 63% of the patients; 44 patients received chemoradiotherapy preoperatively and 19 patients received chemoradiotherapy postoperatively.

Patients were staged according to Western parameters [7] using the surgical specimens from the TME procedures, including only mesorectal lymph nodes. In terms of tumor invasion, four patients had pT1 tumors, 27 patients had pT2 tumors, 47 patients had pT3 tumors, and 22 patients had pT4 tumors. Mean tumor size was 4.5 cm, with a median of 4.2 cm, ranging from 0.8 to 15.8 cm. Mean mesorectal lymph node count was 12.2, and mean RLPN count was 11.9. A total of 2401 lymph nodes were examined. Patient distribution by stage and survival curves is shown in Figure 1. Survival at 60 months of follow up for stage I patients was 100%, 88.8% survival was noted for stage II patients, and 46.5% survival was observed for stage III patients (P = 0.0027).

Pelvic recurrence occurred in 12.0% of the study group, in two patients with pT2 tumors and in 10 patients with pT3/pT4 tumors. Of these 12 patients with pelvic recurrence, five patients had metastases to RLPNs. Therefore, the pelvic recurrence rate was 7.4% in pT2 tumor patients, 14.5% in pT3/pT4 tumor patients, and 29.4% in patients with metastases to RLPNs. According to TNM stage, pelvic recurrence occurred in 11.9% of stage II patients and in 14.7% of stage III patients. At the end of the follow-up period, of the patients with pelvic recurrence, seven patients died due to cancer progression, two patients were alive with distant visceral metastases, and three patients were alive without cancer after salvage surgery and chemotherapy. At 61 months of follow up, 65.5% of the patients in the cohort remained alive and without pelvic recurrence.

RLPL identified 58 metastatic RLPNs in 17 patients, with an incidence of 17%. Figure 2 shows the Kaplan–Meier survival curves of patients with and without metastases to RLPNs. The 50-month follow-up survival of patients with metastases to RLPNs was 28.6 versus 84.5% for patients without metastasis to RLPNs (log-rank P < 0.0001). The hazard mortality cumulative risk of patients with and without metastases to RLPNs was compared in Figure 3.

Seven patients with stage II disease had metastases to RLPNs. Figure 4 shows the survival curves of these patients compared to TME stage II patients without metastasis to RLPNs. At the 50-month follow up, 97.1% of TME stage II patients without metastasis to RLPNs were alive versus 33.3% of TME stage II patients with metastases to RLPNs (log-rank P < 0.0001).

Metastases to RLPNs were detected in 10 TME stage III patients, and the survival of these patients was compared to TME stage III patients without metastasis to RLPNs in Figure 5. Survival of TME stage III patients without metastasis to RLPNs was 68.9% after 50 months, compared to 21.9% for patients with metastases to RLPNs (log-rank P = 0.0237).

Distant metastases occurred in 19% of the cohort; none TNM stage I patient had distant metastases, they occurred in 16.9% of TNM stage II patients, and 26.5% of TNM stage III patients. Six (32.3%) of the 17 patients with metastases to RLPNs developed distant metastases. Only three patients with pelvic recurrence presented distant metastases and they did not have metastases to RLPNs. Patients who developed distant metastases during the follow up had a 60-month survival of 37.3% compared to 85.9% for patients without distant metastases.

**DISCUSSION**

The Aristides Maltez Hospital is a philanthropic institution that treats low-income patients in the public health system. Patients are often malnourished and with a low level of formal education. This information is relevant, as it might have affected the surgical morbidity results. The female predominance in this cohort should not be attributed to a selection bias, it occurs at our institution as seen in our previous publications [8,9,11].

The present study indicates acceptable morbidity and surgical mortality related to RLPL using the nerve preservation technique. The results are considered acceptable as they were similar to early morbidity and mortality rates of patients submitted only to TME in our institution. The high ICU stay is attributed to institutional protocol of indicating ICU to patients over 70 years of age and with associated diseases as hypertension and diabetes. The late morbidity, evaluated at the end of the follow up, is also acceptable, as it is comparable to other published results that indicate a urinary complication rate of 16% and a male impotency rate of 10% [12].

The higher male impotence rate in this study might be a consequence of the treatment of a large number of patients with large pT4 tumors, the associated pelvic radiotherapy delivered to 63% of the patients, and the age of the male population. Large pT4 tumors frequently invade the hypogastric or pelvic nerves, requiring surgical resection to achieve clear oncological margins. The occurrence of male impotence from pelvic radiotherapy delivered to patients with

**TABLE I. Early Operative Morbidity Related to Total Mesorectal Excision Plus Retroperitoneal and Lateral Pelvic Lymphadenectomy With Pelvic Autonomic Nerve Preservation in the Treatment of Rectal Adenocarcinoma Patients**

<table>
<thead>
<tr>
<th>Late postoperative morbiditya</th>
<th>Number of patients affected</th>
<th>Number of patients at risk</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical mortality</td>
<td>4</td>
<td>102</td>
<td>3.9%</td>
</tr>
<tr>
<td>Total surgical complications</td>
<td>34</td>
<td>102</td>
<td>33.3%</td>
</tr>
<tr>
<td>Anastomotic leak</td>
<td>6</td>
<td>49</td>
<td>12.2%</td>
</tr>
<tr>
<td>Wound infection</td>
<td>23</td>
<td>102</td>
<td>22.5%</td>
</tr>
<tr>
<td>Aponeurosis suture dehiscence</td>
<td>10</td>
<td>102</td>
<td>9.8%</td>
</tr>
<tr>
<td>Severe bleeding</td>
<td>6</td>
<td>102</td>
<td>5.9%</td>
</tr>
<tr>
<td>Reoperation</td>
<td>18</td>
<td>102</td>
<td>17.6%</td>
</tr>
<tr>
<td>Respiratory infection</td>
<td>4</td>
<td>102</td>
<td>3.9%</td>
</tr>
<tr>
<td>Sepsis</td>
<td>3</td>
<td>102</td>
<td>2.9%</td>
</tr>
<tr>
<td>Urinary infection</td>
<td>2</td>
<td>102</td>
<td>2.0%</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>1</td>
<td>102</td>
<td>1.0%</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>1</td>
<td>102</td>
<td>1.0%</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>1</td>
<td>102</td>
<td>1.0%</td>
</tr>
<tr>
<td>Severe edema of lower limbs</td>
<td>1</td>
<td>102</td>
<td>1.0%</td>
</tr>
</tbody>
</table>

aEarly postoperative morbidity occurred within 30 days of surgery.

**TABLE II. Late Postoperative Morbidity Related to Total Mesorectal Excision Plus Retroperitoneal and Lateral Pelvic Lymphadenectomy With Pelvic Autonomic Nerve Preservation in the Treatment of Rectal Adenocarcinoma Patients**

<table>
<thead>
<tr>
<th>Late postoperative morbiditya</th>
<th>Number of patients affected</th>
<th>Number of patients at risk</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total late morbidity events</td>
<td>25</td>
<td>97</td>
<td>25.8%</td>
</tr>
<tr>
<td>Male sexual impotence</td>
<td>6</td>
<td>37</td>
<td>16.2%</td>
</tr>
<tr>
<td>Fecal incontinence</td>
<td>4</td>
<td>40</td>
<td>10.0%</td>
</tr>
<tr>
<td>Severe pelvic pain</td>
<td>8</td>
<td>97</td>
<td>8.1%</td>
</tr>
<tr>
<td>Incisional hernia</td>
<td>7</td>
<td>97</td>
<td>7.2%</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>6</td>
<td>94</td>
<td>6.4%</td>
</tr>
<tr>
<td>Retropubic ejaculation</td>
<td>2</td>
<td>37</td>
<td>5.4%</td>
</tr>
<tr>
<td>Parastomal hernia</td>
<td>4</td>
<td>97</td>
<td>4.1%</td>
</tr>
<tr>
<td>Colostomy prolapse</td>
<td>4</td>
<td>97</td>
<td>4.1%</td>
</tr>
</tbody>
</table>

aLate postoperative morbidity occurred more than 30 days after operation and until the end of follow up.
rectal adenocarcinoma has also been reported [13,14]. The Japanese protocol for postoperative radiotherapy is much more restricted, and might favor their results [8]. The male population of this cohort had a mean age of 56 years and a median age of 57 years. It is well known that a higher frequency of postoperative male impotence after rectal resection is observed among patients older than 50 years of age [13,15].

The incidence of metastases to RLPNs in this cohort demonstrates that the lymphatic dissemination of cancer cells though RLPNs is not specific for Japanese patients. It raises a debate that Western rectal cancer treatment does not address this issue, as metastases to RLPNs are not surgically detected because RLPL is not routinely performed.

Metastases to RLPNs predicted an unquestionable unfavorable prognostic outcome in the patients of this cohort, related to poor survival and a high rate of pelvic recurrence. Previous studies have shown a 5-year survival of 39.8% in patients with RLPNs metastases [5]. This study has an even more unfavorable result with a 50-month survival rate of 28.6% in patients with metastases to RLPNs. Pelvic recurrence rate of patients with RLPNs metastases has been reported.

Fig. 1. Kaplan–Meier survival curves according to the UICC/AJCC Tumor Nodes Metastasis-TNM cancer staging system. Note: Staging was performed exclusively with the surgical specimens obtained with the total mesorectal excision.

Fig. 2. Kaplan–Meier survival curves of adenocarcinoma rectal patients with and without metastases to retroperitoneal or lateral pelvic lymph nodes (n = 100).

Fig. 3. Hazard mortality cumulative curves of adenocarcinoma rectal patients with and without metastases to retroperitoneal or lateral pelvic lymph nodes—Nelson-Aalen estimator (n = 100).
to be 26.1% [5], whereas this study demonstrated a 29.4% recurrence rate. As there were only 17 patients with metastases to RLPNs, further multicenter studies should evaluate the oncological outcome of rectal adenocarcinoma patients with metastases to RLPNs.

It is important to note that the present cohort included patients without metastases to mesorectal lymph nodes who had metastases to RLPNs. If RLPLs were not performed, some patients of this cohort who were considered to have stage II disease would not have been treated with adjuvant chemoradiotherapy.

These results suggest that low rectal adenocarcinoma patients with metastases to RLPNs should be identified so that they can be staged in a different manner; they should not be included in TNM stage II or III. A more intense adjuvant treatment for patients with RLPNs metastases could be delivered as they have unfavorable prognostic outcome. Currently, the only way to stage these patients is to perform RLPLs, as preoperative exams do not properly identify RLPNs metastases. RLPL is a safe surgical procedure, as the morbidity and mortality rates of this study indicate. RLPLs should be considered in patients without distant visceral metastases and with greater risk of RLPNs metastases. Our previous publication shows that such patients have metastases to mesorectal lymph nodes, pT3/pT4 tumors, high levels of carcinoembryonic antigen (average of 30.6 ng/ml, median of 9.9 ng/ml), and large tumors (mean size: 5.5 ± 3.2 cm) [8].

This study could not evaluate whether RLPL had a therapeutic effect or if it should be only indicated for proper patient staging. The survival rate of patients with metastases to RLPNs was similar to that of TNM stage IV patients. Would the survival rate of the patients with RLPNs metastases be worse if RLPLs were not performed? This present study cannot answer this question. With low morbidity and mortality rates, it is rational to consider RLPL in patients with metastases to RLPNs. This method might improve quality of life by decreasing pelvic recurrence in these patients. At the end of follow up, 29.4% of patients with metastases to RLPNs in the present study were alive and without pelvic recurrence, and 70.6% of patients with metastases to RLPNs completed their follow up without pelvic recurrence.

CONCLUSIONS

RLPL has acceptable morbidity and mortality rates. Metastases to RLPNs indicated unfavorable survival and considerable pelvic recurrence rates in patients of this cohort. Patients with metastases to RLPNs should be identified for proper surgical staging and adjuvant treatment.

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REFERENCES


