Lateral Node Dissection in Locally Advanced Rectal Cancer with Radiologically Detected Extramesorectal Node Metastasis

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Abstract

Rationale: The incidence of lateral node metastasis in rectal cancer ranges from 10-23%. Patients with lateral node deposits show poor outcome, yet lateral node dissection may provide a favorable prognostic value with respect to local disease control.

Aim: The purpose of the study is to evaluate the clinical outcome of patients that underwent lateral node dissection for radiologically detected extramesorectal nodes.

Methods: This study ran from 2007 through 2011 and involved 75 patients with stage II and III rectal cancer who received neoadjuvant long course chemoradiation followed by total mesorectal excision and concomitant lateral node dissection for radiologically detected extramesorectal nodal metastasis. MRI and multi detector CT were used to assess primary tumour stage, lateral, mesorectal and paraaortic lymph nodes. Lymph nodes larger than 0.5cm at the short-axis diameter, with speculated edges or heterogenic pattern was considered malignant. PET CT was used in uncertain diagnosis.

Results: The perioperative mortality occurred in 3% and surgical morbidity in 16%. The positive predictive value (PPV) for the radiologically diagnosed extramesorectal nodal metastasis was 93.3% for lateral nodes and 55% for the paraaortic and mesorectal nodes. Pathological examination revealed N0 in 26%, positive lateral (LA), Mesorectal & Para-aortic (MP), lateral and mesorectal-paraaoartic nodes (LA&MP) (26%-33% and 15%) respectively. The 5-year cancer specific survival rate in patients with lateral, Mesorectal, lateral and Mesorectal nodes was (46.2%, 43.1% and 18.3%). The 5-year disease free survival (DSF) in patients with the same groups was (39.3%, 32% and 16.1%) respectively.

Conclusion: The prognostic significance, the associated morbidity and the false positive results of radiological diagnosis of lateral node disease should decide the role of lateral node dissection in rectal cancer.

Key Words: Lateral node – Metastasis –Rectal cancer.

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Introduction

PELVIC recurrence in rectal cancer is a devastating problem for both surgeons and patients. Following Total Mesorectal Excision (TME), the positive circumferential resection margin has been recognized as a major cause of loco regional recurrence. Nevertheless, in locally advanced rectal cancer the incidence of extra mesorectal spread to lateral lymph nodes ranges from 10%-25%. Such nodes are not removed with TME [1-2].

In early 1950, Lymph node drainage was shown to flow along the internal iliac artery, and lateral node dissection was attempted aiming at better local disease control [3-8]. In 1975, Koyama et al., reported that lateral node dissection decreased local recurrence. In 1980s, several studies showed that extended lymph node dissection including the lateral nodes inhibits local recurrence and has a positive impact on overall survival [9-13]. More than 40% of locoregional recurrence in patients with lateral lymph node metastasis are developed without distant metastasis [14]. Hence Lateral node dissection became a standard technique for surgical management of locally advanced rectal cancer below peritoneal reflection aiming at minimizing local recurrence and improve overall survival. Routine practice of lateral node dissection is still debatable as nearly less than one quarter of patients with locally advanced rectal cancer have lateral node involvement [10-13]. Lateral node dissection was associated with pelvic autonomic nerve damage with a high incidence of genitor-urinary dysfunction [16-18]. To minimize such drastic complications, Hojo et al. [19] introduced a procedure of Pelvic autonomic nerve preservation concomitantly performed with lateral node dissection. This procedure minimized the urinary and sexual disturbance to
Recent studies showed that this combined approach was useful and reported a decrease in local recurrence rates by about 50% and increase 5-year survival rates by 8%.

According to the Japanese Classification of colo-rectal carcinoma [21], the regional areas of the rectum were divided into four areas namely; 1- Mesorectal area, 2- Superior rectal artery area (SRA), 3- Inferior mesenteric artery area (around the IMA between its origin and the left colic artery), 4- Lateral pelvic area.

Extramesorectal node dissection refers to dissection of nodes in the paraaortic and lateral pelvic lymph node groups [20]. This includes high ligation of the inferior mesenteric artery at its origin from the aorta. Dissection of all lymphatic around the abdominal aorto-iliac vessels starting from the duodenum and left iliac vein as the upper limit of node dissection down to the iliac vessels.

As for the lateral area, the iliac lymph nodes area outside the mesorectum was divided into the following six regions: The internal pudendal (outside the pelvic plexus), the internal iliac (proximal to the superior vesical artery), the common iliac, the external iliac, the obturator, the presacral area.

Preoperative staging is essential for planning the optimal radical surgery that will be reflected on survival. The diagnostic accuracy of extramesorectal lymph nodes involvement with the conventional radiological modalities such as computed tomography (CT) and magnetic resonance (MRI) have not been satisfying. The prognostic significance of lateral node dissection should be weighed against the possible associated genitor-urinary morbidity.

The aim of this study is to evaluate the clinical outcomes of patients who underwent lateral node dissection based on preoperative radiological detection of Extramesorectal lymph nodes so as to determine the subset group of patients that might benefit from this technique.

**Patients and Methods**

A total of seventy five consecutive patients presented to the outpatient clinic at the National Cancer Institute of Cairo University, were enrolled in this prospective study between 2007 and 2012. Patients were recruited for 36 months from the start of the study and were followed till the end of 2012, with the following inclusion criteria: Rectal Carcinoma ≤ 1 5cms from the anal verge as proven by colonoscopic biopsy. Locally advanced resectable rectal cancer (stage II and III) as evaluated by pelvic Magnetic Resonance Imaging (MRI) coupled with transrectal ultrasound in some cases, radiologically suspicious lymph nodes in the extramesorectal nodes namely the paraaortic and lateral pelvic nodes. The exclusion criteria were: Metastatic disease to solid organs as liver, tumors invading neighboring organs as prostate, bladder in males or uterus in females.

The study was conducted after being approved by the Institutional ethical committee and an informed consent was obtained from patients regarding morbidity of surgical technique and chemo radiation.

A preoperative staging work up was performed using chest X-ray, abdominal computerized tomography (CT) and pelvic MRI. MRI was used for detection of lateral node disease, as for the paraaortic lymph nodes CT was basically used. PET-C.T. scan was performed in a group of patients with uncertain diagnosis of metastasis in either the paraaortic-mesorectal or lateral groups of lymph nodes.

Radiological criteria of lateral Lymph node involvement were defined as; Lymph node of ≤0.5cm at its short axis diameter, Speculated or indistinct border, a mottled heterogenic nodal pattern as detected by high resolution MRI, a multislice C.T or as a lymph node showing positive uptake in PET C.T scans. As for the location of rectal cancer, tumours located 15cms from the anal verge were defined as upper rectal cancer, whereas those between 10 and 15cms were defined as mid rectal tumors and tumours ≥5cm from the anal verge defined as low rectal tumours.

According to the status of lymph node metastasis, patients were classified into four groups:

- Patients without lymph node metastasis (NO),
- Patients with Mesorectal & Para-aortic node metastasis (MP),
- Patients with lateral node metastasis (LN),
- Patients with lateral and Mesorectal–paraortic node metastasis (LN+MP).

**Patients characteristics and baseline parameters consisted of the following variables:**

- Age, sex, tumour site, node status, residual tumours following resection, histopathological predictor factors for local recurrence (as CRM, lymphovascular invasion), type of neoadjuvant treatment received and final pathological reports regarding node status.

**Surgical technique:**

In upper rectal cancer, subtotal mesorectal excision was carried out with at least 4cms below
the resected tumour, whereas in mid and low rectal cancer, total mesorectal excision was carried out. Sharp dissection with proper visualization of the pelvic nerves was mandatory for preservation of the genitourinary function. Lymph node dissected by the classical mesorectal excision were labeled as mesenteric nodes (PAND), nodes harvested in the lateral pelvic group were labeled as extramesorectal nodes (LPND). Preoperative chemo radiation was administered using the regimen of 5-Fluorouracil and leucovorin with concomitant radiation. The preoperative radiation was delivered to the entire pelvis covering from L5 level to 3cms below the lower margin of the tumour alongside the bilateral pelvic walls. The dose was 45Gy in 25 fractions followed by a 5.5Gy in 3 fractions boost to the primary tumour within 6 weeks.

To evaluate the response to the neoadjuvant therapy, MRI scans were performed 2-4 days prior to surgery. All patients underwent curative resections including high ligation of IMA and lateral pelvic node dissection (LPND) and (PANP) with total mesorectal excision. The median interval between completion of neoadjuvant CRT and surgery was 8 weeks (4-12 weeks) for better chance of complete down staging.

Sphincter Saving Resection (SSR) was performed to 80% of patients while the remaining 20% underwent extra-levator abdominoperineal resection (EL-APR). All the pre and post CRT MRI images were retrospectively evaluated for clinical and pathological results. As for the lateral lymph nodes, the shortest axis diameter of lateral nodes was recorded and nodes considered clinically positive if the diameter were ≥5mm. The assessment of the clinical and radiological response to neoadjuvant CRT was defined as at least 30% decrease in its longest diameter. Patients were followed-up every three months for the first two years in the postoperative period and every six months for up to five years thereafter. For the evaluation, a clinical examination, Carcino Embryonic Antigen (CEA) levels, chest X-ray were performed during follow-up visits. Follow-up abdominopelvic C.T. scan was done in the first six months follow-up period and then on annual basis. MRI pelvis was planned if C.T. failed to detect suspicious lesions and PET.C.T. Scan was resorted to in selected patients with equivocal results.

Results

The patient characteristics are all summarized in Table (1).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male: Female ratio</td>
<td>1.8:1</td>
<td></td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>48.3±9.3</td>
<td></td>
</tr>
<tr>
<td>Tumour site:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper Rectum</td>
<td>17</td>
<td>23</td>
</tr>
<tr>
<td>Mid and Lower Rectum</td>
<td>58</td>
<td>77</td>
</tr>
<tr>
<td>Pre-operative radiological LN diagnosis:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lateral node</td>
<td>25</td>
<td>33</td>
</tr>
<tr>
<td>Para-aortic node</td>
<td>23</td>
<td>30</td>
</tr>
<tr>
<td>Lateral and para-aortic node</td>
<td>27</td>
<td>37</td>
</tr>
<tr>
<td>Residual tumour:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R0</td>
<td>64</td>
<td>85</td>
</tr>
<tr>
<td>R1</td>
<td>11</td>
<td>15</td>
</tr>
<tr>
<td>Lymphovascular invasion:</td>
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<td></td>
</tr>
<tr>
<td>Negative</td>
<td>39</td>
<td>52</td>
</tr>
<tr>
<td>Positive</td>
<td>36</td>
<td>48</td>
</tr>
<tr>
<td>Treatment:</td>
<td></td>
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</tr>
<tr>
<td>Neoadjuvant chemoradiation only</td>
<td>32</td>
<td>43</td>
</tr>
<tr>
<td>Neoadjuvant chemoradiation + postoperative</td>
<td>43</td>
<td>57</td>
</tr>
<tr>
<td>Pathological node metastasis:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>20</td>
<td>26</td>
</tr>
<tr>
<td>Mesorectal Para-aortic node metastasis (MP)</td>
<td>25</td>
<td>33</td>
</tr>
<tr>
<td>Lateral pelvic node (LA)</td>
<td>20</td>
<td>26</td>
</tr>
<tr>
<td>Para-aortic + lateral (MP&amp;LA)</td>
<td>11</td>
<td>15</td>
</tr>
</tbody>
</table>

Oncological outcome:

The frequency and prognostic impact of lateral node involvement:

Lateral node involvement was pathologically evident in 33 patients (44%). The internal iliac and obturator groups were among the most commonly involved regions. The Paraortic node involvement alongside mesorectal nodes were evident in 25 patients (33%) (Fig. 1).

The 5 year survival rate in patients with lateral node involvement (LA) was 46.2% (95% CI: 78.4-98.9% CI: Confidence Interval). Similarly, The 5 year survival rate for patients with paraaortic lymph nodes (MP) metastasis was 43% (CI 51.3%-77.4%). As for the disease free survival rate-DFS-in patients with lateral (LA) and paraaortic node (MP) metastasis, it was 39.3% and 32% respectively (Fig. 2).

Sixteen patients (20%) harbored both paraaortic and lateral nodes involvement, those patients had the worst oncological outcome compared to the other groups. The 5 year survival rate and the disease free survival rates were 18.3% and 16. 1 % (p=0.070) respectively.

Twenty patients (26%) with negative nodes (NO) showed a 5 year survival rate of 100% (p=0.376), the disease free survival rate was 72.4% (p=0.070).
Groups

- LA
- PA
- PA & LA
- N0
- LA-censored
- PA-censored
- PA & LA-censored
- N0-censored

**Fig. (1)**

**Fig. (2)**

**Fig. (3):** Pelvic MRI & Endo Rectal MRI for Lateral Node Detection.

**Fig. (4):** Comparative outcome of the radiological and pathological outcome.
The comparative results of the preoperative radiological imaging and the postoperative pathological status of lymph node involvement were calculated and expressed as Positive Predictive Value (PPV) for each group. PET C.T. scans were referred to in eight cases of suspicious paraaortic and lateral pelvic nodes. PET scans revealed hot uptake in all of the cases with a PPV of 100%. The Positive Predictive Value for lateral node metastasis was 31 out of 33 (93.9%), meanwhile the PPV for paraaortic and mesorectal nodes was 36 out of 65 (55%).

Perioperative morbidity and mortality:

Perioperative mortality occurred in two patients (3%) in the first 30 days postoperatively; one patient developed respiratory failure due to postoperative atelectasis whereas the other one developed septic shock due to fulminant pelvic sepsis following anastomotic leakage.

A total of 12 patients (16%) developed postoperative morbidity within 30 days, namely urinary tract dysfunction (n=4), anastomotic leakage (n=3), respiratory complications (n=3), intestinal obstruction (n=1) and wound infection (n=1).

Table (2): Perioperative mortality and morbidity 30 postoperative days.

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Morbidity total number</td>
<td>12/75</td>
<td>16</td>
</tr>
<tr>
<td>Urinary dysfunction</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Anastomotic leakage</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Respiratory complications</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Intestinal obstruction</td>
<td>1</td>
<td>1.3</td>
</tr>
<tr>
<td>Wound infection</td>
<td>1</td>
<td>1.3</td>
</tr>
</tbody>
</table>

Discussion

Accurate preoperative staging of rectal cancer is important to choose the proper treatment modality. The lateral pelvic lymph node status is an important factor in determining the extent of node dissection and type of surgery. Different diagnostic modalities as transrectal ultrasound (TRUS), Computerized Tomography (C.T.) and Magnetic Resonance Imaging (MRI) are used for tumour and node staging.

MRI can show lateral lymph node status, it could give useful information on the enlargement of perirectal, lateral pelvic nodes. This finding could justify extended lateral pelvic node dissection that carries the risk of pelvic autonomic nerve damage for selected cases avoiding unnecessary damage for the rest of the patients.

In rectal cancer lymph node metastasis is considered an important prognostic factor regarding the oncologic outcome. Both the number of involved nodes and their locations are significant. The treatment strategy for lateral pelvic metastasis detected radio logically in the preoperative work up remains a debatable topic. Regarding the preoperative evaluation of lateral node status, Kim et al. [23], stated that the positive predictive value falls to 29%. With the advancement of imaging technology, MRI imaging alongside the mounting experience in interpreting the nodal status, diagnostic criteria for lateral pelvic lymph node metastasis led to improvement of the PPV and accuracy of MRI in detecting such nodes up to 100% and 84% respectively [24].

In our study, we managed to demonstrate an improvement of PPV for both lateral and paraaortic node staging. A devoted rectal radiologist applying the standard diagnostic criteria as well as utilizing updated imaging modalities as high resolution MRI and multislice C.T. scans all led to improvement of PPV outcome.

Lateral lymph node metastasis was found in 23.5% of patients with lymph node metastasis in the mesorectum. In patients with negative mesorectal nodes, 20.2% had metastasis only in the lateral pelvic group. Such findings indicate that TME alone is insufficient to address potentially metastatic lateral lymph nodes, that were associated with a recurrence rate of 58.1%. The 5 year survival rate for patients that underwent radical lateral node dissection for metastatic disease reached 42%. Regarding the paraaortic node dissection, little evidence is available concerning its impact on survival. Most of the studies that showed survival benefit of paraaortic node dissection were in the era before multimodality therapy approach [25].

In a retrospective study by Min et al., patients who underwent surgical resection for paraaortic lymph nodes had a survival benefit over patients who received chemotherapy or chemoradiation alone, in patients with radiologically diagnosed paraaortic lymph nodes. The impact of lateral node dissection on the 5 year disease free survival was 45% suggesting its role in prevention of intrapelvic recurrence, the potential benefit of preoperative chemoradiation over lateral pelvic node dissection has been a debatable issue [26]. Another study by Kim et al., reported a higher incidence of local recurrence rates in patients with TME and lateral node dissection compared to those with TME plus postoperative chemoradiation [27].
Nagawaa et al., observed in their randomized prospective trial no significant differences in survival and recurrence between patients who received preoperative radiation with lateral node dissection and those without lateral node dissection. The study of stated that lateral lymph node dissection was not indicated for patients with preoperative radiation for rectal tumours [28].

In the current study, the incidence of lateral pelvic node involvement was 26%. Patients with preoperative radiological diagnosis of lateral pelvic node involvement showed a 5 year survival and disease free survival rates of 46.2 and 39.3% respectively.

The PPV for lateral node metastasis was 93.9%, higher than the PPV for mesorectal and paraaortic node metastasis of 55% since we coupled MRI and C.T. in lateral node detection while C.T. was solely applied for paraaortic lymph node assessment. PET.C.T. scan was of additional benefit for improvement of PPV for nodal status in all questionable and ambiguous cases.

In such conditions, extended lateral node dissection with concomitant pelvic autonomic nerve sparing could be justified as an additional surgical treatment in patients with preoperatively detected lateral lymph node deposits.

The accuracy of nodal status using MRI has been reported as less reliable than for local tumour staging [29]. No consensus has been reached regarding the size criteria predictive of metastatic lymph nodes.

Nevertheless, in diagnosis of metastatic lymph nodes using MRI, the lymph node size is still the most reliable parameter and 5mm is the most evident criterion for the upper limit of normal lymph nodes [30]. Patients with lateral lymph node size of ≥1 0mm and a P NO or lateral node size of <5mm are a potential subgroup of patients who might benefit from lateral node dissection.

The technique of extended lateral node dissection adopted in our study was different from the original and standard one performed by the Japanese group. In our study we limited the lateral pelvic dissection to the group of pelvic nodes detected preoperatively by radiological imaging.

In a recent study Kim et al., demonstrated that lateral pelvic recurrence was the commonest pattern of locoregional recurrence after neoadjuvant chemotherapy followed by TME alone. In his study, the incidence of lateral pelvic recurrence in patients with positive lateral nodes compared to those with negative lateral nodes was 26.6% vs 2.3% (p-value r=0.01). Therefore such patients with Radiologically suspicious lateral pelvic nodal metastasis require additional surgical treatment alongside the TME following neoadjuvant chemotherapy resulting in better local disease control and on oncological outcome since such disease could be potentially curable regional disease rather than a metastatic one [31].

In our study, patients with preoperatively diagnosed paraaortic nodal metastasis who underwent paraaortic nodal dissection had a 5 year survival and disease free survival rates of 40.7% and 32% respectively.

Patients who harbored synchronous Lateral pelvic and paraaortic nodes demonstrated poor prognostic outcome with overall 5 year survival and disease free survival of 18.3% and 16.1% respectively.

 Patients with preoperative radiological diagnosis of negative mesorectal and extramesorectal nodes with P NO demonstrated a survival benefit. The 5 year survival and disease free survival of 100% and 72.4% respectively.

The main drawback of this surgical technique is the genitourinary dysfunction associated with lateral pelvic node dissection in addition to other morbidities.

Pelvic autonomic nerve preservation was concomitantly performed with lateral node dissection, remarkably minimizing the genitourinary dysfunction without jeopardizing the oncological outcome. The outcome of our cases in comparable to other studies.

Conclusion:
Based on our results, rectal cancer patients with extramesorectal node disease represent a subset group of patients with poor prognosis in need of more extensive and comprehensive treatment. Lateral pelvic node dissection is performed to suppress local pelvic recurrence. It is therefore essential to identify patients who would benefit from the technique. Accurate preoperative staging with pelvic MRI can determine the pelvic lymph node status. This might be able to help surgeons in the choice of the appropriate extent of dissection. Nevertheless, the optimal management for this group of patients remains debatable, mandating further clinical research to explore new imaging modalities for nodal detection.
References


