

## Extended versus standard pelvic lymphadenectomy in radical cystectomy for urinary bladder cancer, a comparative study

Ali Zedan<sup>1</sup> (MD. , MARCS, Haisam Atta<sup>2</sup>, MD. , Adel Gabr<sup>3</sup>, MD. and Tareq Salah<sup>4</sup>, MD.

<sup>1</sup>Department of Surgical Oncology,, South Egypt Cancer Institute (SECI), Assiut University, Egypt

<sup>2</sup>Department of Oncoradiology, South Egypt Cancer Institute (SECI), Assiut University, Egypt

<sup>3</sup>Department of Medical Oncology, South Egypt Cancer Institute (SECI), Assiut University, Egypt

<sup>4</sup>Department of Clinical Oncology, Faculty of Medicine, Assiut University, Egypt

[tareqsalah41@yahoo.com](mailto:tareqsalah41@yahoo.com)

**Abstract: Objective** compare extended lymphadenectomy to standard lymphadenectomy regarding occurrence of complications, operative duration blood transfusions, Cancer-specific survival (CUSS), recurrence-free survival (RFS), Number of total and positive LN yield, density, and effect on survival. **Material and Methods:** We retrospectively identified 204 patients had urinary bladder cancer confined to bladder wall from the period January 2000 to January 2013 underwent radical cystectomy in South Egypt Cancer Institute Assiut university, patients were divided into 2 groups Group I (147 patients) had a standard pelvic lymph node dissection (PLND) Group II (57 patients) had Extended PLND in each group we evaluated the Oncological, operative data, Peri-operative and late complications. **Results:** There is improvement in recurrence free survival (RFS) in group II with percentage 84%, 73% and 67% for 2, 3 and 5 years respectively where that of Group I is 77%, 67% and 54%. **Conclusions:** performing an extended lymphadenectomy till the origin of inferior mesenteric artery For bladder cancer is potentially curative with improved RFS, DSS survival without adding to the overall operative time and morbidity compared with a standard PLND

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### 1. Introduction

In patients with cancer bladder, the incidence of lymph node involvement is approximately one third to one fourth of patients with bladder cancer and is correlated with increasing tumor stage<sup>1</sup>.

One of the most important surgical factors is the extent of the lymphadenectomy where the debate exists regarding the boundaries of lymphadenectomy as limited dissection (cephalad boundary at the common iliac bifurcation external iliac and obturator region bilaterally) which is associated with less accurate staging and a relative poor oncological outcome while an extended lymphadenectomy is defined when the lymph node dissection is extended up to the inferior mesenteric artery (IMA) including the distal Para aortic and paracaval lymph nodes with removal of the presacral nodal, these boundaries potentially guarantee the complete removal of the primary, secondary, and tertiary lymph nodes improving the detection of tumor involved lymph nodes.<sup>2-12</sup>

Extended PLND ensures more accurate staging and prognostic information and has therapeutic benefits in a select subset of patients with positive and even in patients with negative lymph nodes provides excellent local control and long-term survival for extended nodal dissection, allowing

adjuvant chemotherapy to be offered early when<sup>1,7</sup>. Preoperatively, lymph nodal assessment is done by computed tomography (CT) and magnetic resonance imaging (MRI) which, at times can be false negative in approximately 25% of cases. Preoperative imaging studies CT scan or an MRI will miss microscopic nodal metastasis in up to 70% of the patients<sup>13</sup>. Significant numbers of patients have lymph node metastasis above the boundaries of standard LND<sup>8</sup>. 9-19% of lymph node metastases also included nodes above the aortic bifurcation, while 5-8% of nodal metastases involved the presacral region.<sup>10</sup> A standard lymph node dissection (LND) would have failed to address 74% of the positive nodes and 7% of these patients 'pathologies would have been falsely reported as negative. Lymphatic trunks leading from the pelvic LN presacral LN (lymph nodes). subsequently drain into more proximal common iliac LNs and then to aortocaval LNs.<sup>14</sup> The common iliac LNs are now considered part of the regional LNs The 2010 seventh edition changes to the AJCC. TNM staging system<sup>10, 15</sup> Recently, lymph node density, even in the presence of positive lymph nodes, Versus further prognostic value in predicting disease-specific survival<sup>16</sup> patients with lymph node metastases following radical cystectomy. These prognostic factors include the extent of the primary bladder

tumor (p-stage), the total number of lymph nodes involved with tumor (tumor burden), the extent of lymphadenectomy (number of lymph nodes removed), and lymph node density.<sup>3</sup>

## 2. Material and Methods

We retrospectively identified 204 patients had bladder cancer underwent radical cystectomy in South Egypt Cancer Institute Assiut university<sup>17</sup> in the period from January 2000 to January 2013, with almost the same pathologic stage with tumors confined to the bladder wall (tumor stage pT3a or less).

### I-surgical technique of lymphadenectomy

Patient were divided into 2 groups ; **Group I** (147 patients) underwent a standard pelvic lymph node dissection (PLND) where the standard lymphadenectomy is bounded distally by the circumflex iliac vein and femoral canal to include Cloquet's node, laterally by the genitofemoral nerve, medially by the bladder and internal iliac vessels, posteriorly by the obturator fossa, the pelvic floor inferiorly, the floor of the obturator fossa down to the superior and inferior vesical arteries; and proximally by crossing of the ureter over the common iliac, (midpoint, distal aspect of) the common iliac (figure 1) according to the surgeon this was sent to the pathologist in separate packages. Submitted as separate packets or en bloc (six nodal packages)

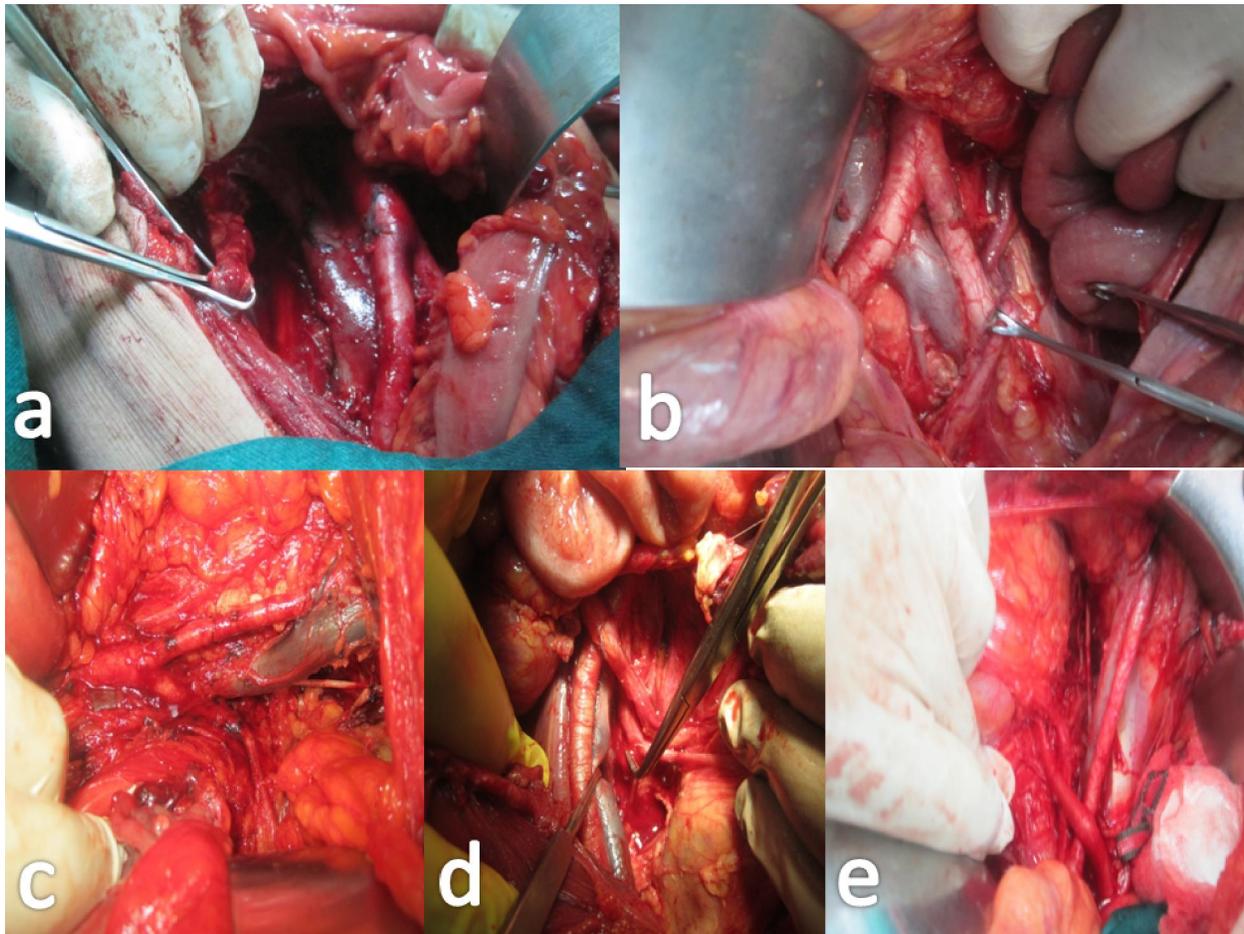


Figure (1) operative photo showing (a) Common Iliac Nodes (b) Crossing of ureter over common iliac artery, (c) External Iliac Nodes (d) Internal iliac nodes and (e) Obturator Nodes

While **Group II** (57 patients) who underwent Extended pelvic lymph node dissection (PLND) as the extended PLND has been variously defined to include a more cephalad proximal boundary up to the inferior mesenteric artery (figure2) include presacral

nodes, sent to pathology in ( ten nodal packages). The LN specimen from each anatomical location was separately examined.

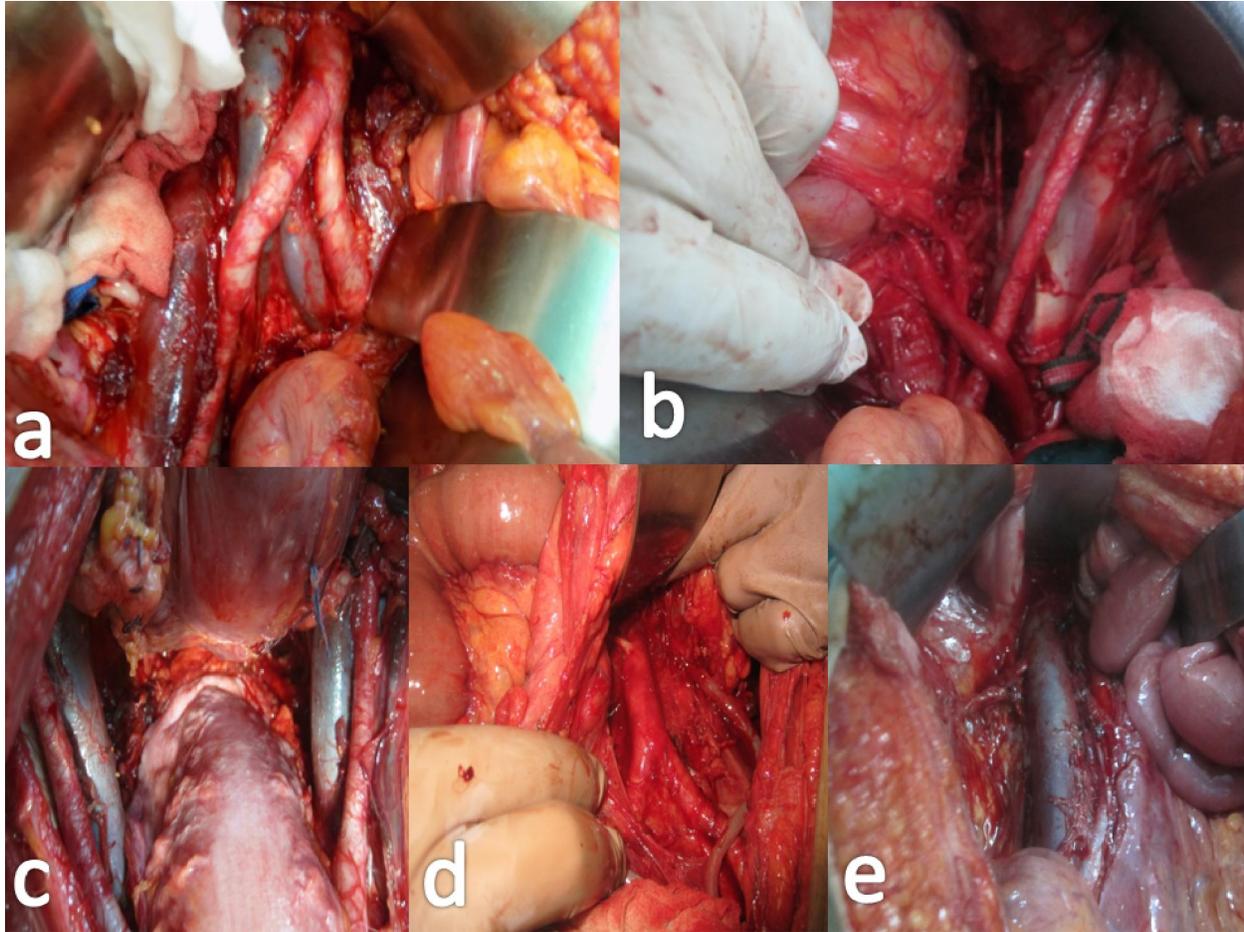


Figure (2) operative photo showing (a) Extended PLND, (b) Standard Lymphadenectomy (c) Bilateral Iliac Lymphadenectomy, (d) Extended proximal to inferior mesenteric artery and (e) Para caval nodes

Demographic data of all the patients were retrieved from the patients' case sheets. .

#### II-Pathological evaluation of excised lymph nodes

The total number of lymph node count is recorded. the positive excised lymph node is determined, lymph node density which is defined as the total number of positive lymph nodes (tumor burden) and the total number of lymph nodes removed (extent of lymphadenectomy).<sup>18</sup>

#### III-Patient follow up

Oncological follow-up included Clinical, Laboratory and imaging assessments ;Our patients were followed regularly every 3 months for 2 years, every 6 months for next 3 years and then at yearly intervals thereafter. The evaluation was done by clinical history, physical examination, urinalysis and culture sensitivity, blood chemistry and imaging by abdominal ultrasonography and with abdominopelvic CT scan and CT chest from 2012 MDCT of

abdomen and pelvis. Evaluating the Oncological outcome, regarding the oncological output response evaluation criteria in solid tumors (RECIST criteria) version 1. 1

#### IV- imaging studies preoperative evaluation and postoperative follow up

Imaging diagnostic procedures ultrasonography, computed tomography (CT), MDCT, magnetic resonance imaging (MRI). where revision of the preoperative images with application of criteria meeting the American Joint Committee on Cancer (AJCC) staging system (7th edition)<sup>19</sup> while the postoperative studies and oncological outcome were evaluated according to RECIST criteria (ver1. 1)<sup>20</sup> for the significance of lymph nodes size the short axis diameter is employed (**Figure3**).

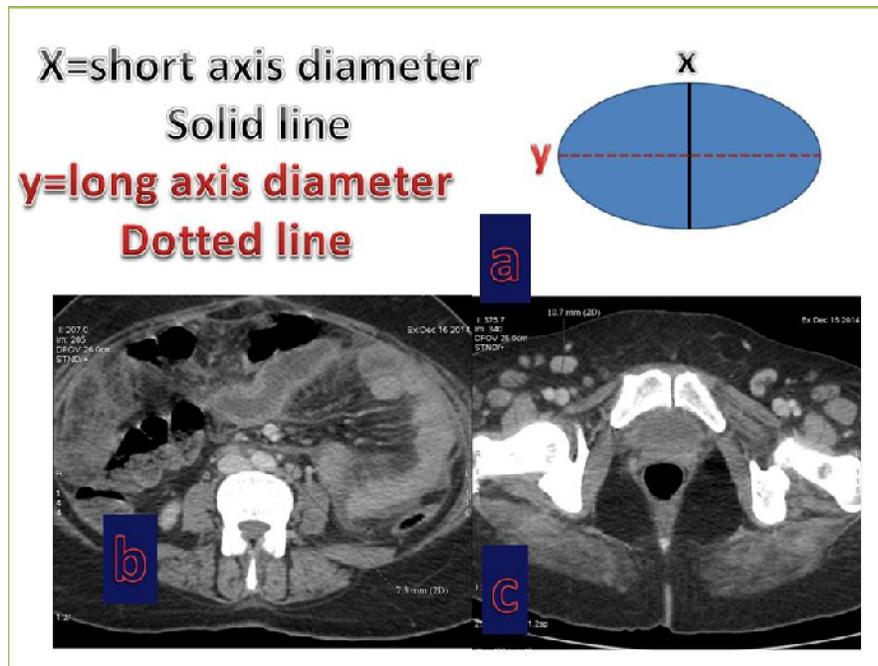


Fig (3) :measurements of lymphadenopathy,where (a) schematic diagram of lymph node measurements as the dotted line [in red] represents long axis diameter while the solid line [in black] represents short axis diameter, (b)shows para-aortic lymph node with short axis diameter 7 mm where (c) shows right inguinal lymph node with short axis diameter 11 mm

Adjuvant chemotherapy was given to the patients with LN involvement and/or T3. .

#### Statistical methods

We compared RFS and CSS for patients following RC/PLND, stratified by the AJCC nodal staging criteria seventh edition. Patients were given a consensus pathologic stage based on the higher stage identified at the time of the transurethral resection or RC. RFS was calculated as the time from surgery to the earliest event of a recurrence, metastasis, or death from disease.

Survival estimates were described using Kaplan-Meier methods. Gender, age, pathologic stage, histology, grade, number of positive lymph nodes, lymph node density, and perioperative chemotherapy were evaluated as predictors of RFS and CSS using multivariate

### 3. Results

No significant statistical significance between the 2 groups as regards mean hospital stay were 9 days for Group I and 10 days for group II ( $p=0.06$ ) or Mean blood loss 1040 ml for a group I and 1130 ML ( $p=0.93$ ) for group II or the percentage early complication 27% in group I and 24 % in group while Mortality percentage is 3% in Both group. In spite that there is increase in the mean operative time about 35 min between the 2 groups as the Mean

operative time 253 minute for group I, 288 minute for group II.

Table. 1: The characteristic properties of patients groups are summarized in

|                                       | Group I | Group II |
|---------------------------------------|---------|----------|
| <b>Number of patients</b>             | 147     | 57       |
| <b>Mean age (Years)</b>               | 59      | 58       |
| <b>Mean hospital stay (Days)</b>      | 9       | 10       |
| <b>Mean operative time in minutes</b> | 253     | 288      |
| <b>Mean blood loss in ml</b>          | 1040    | 1130     |

Table 1: patients' demographics

Mean total lymph nodes counts were 21 (8-39) nodes in a standard PLND and 37 (24-53) nodes an extended PLND with statistical significance ( $p=0.001$ ). Mean positive nodes for group I 2.122 (0-6) and for group II 3.053 (0-9). Nodes. The rate of lymph node metastasis in group I is 21% and 27 % in group II

The 5-year cancer specific survival rates in patients with 25 lymph node or less is 58%, while it is 67% with excised lymph nodes more than 25 respectively. The 5-year RFS rates in the Lymph node density In patients 20% or less is 36% and 17% for lymph node density more than 20 % while The 5-year CSS in patients with a lymph node density in

patients 20% or less and that for lymph node density more than 20%, are 39% and 18% respectively

Regarding the cutoff value of the short axis diameter of metastatic lymphadenopathy, No

significant statistical correlation between pelviabdominal lymph node size and histopathological results. With no reliable cut off value could be employed.

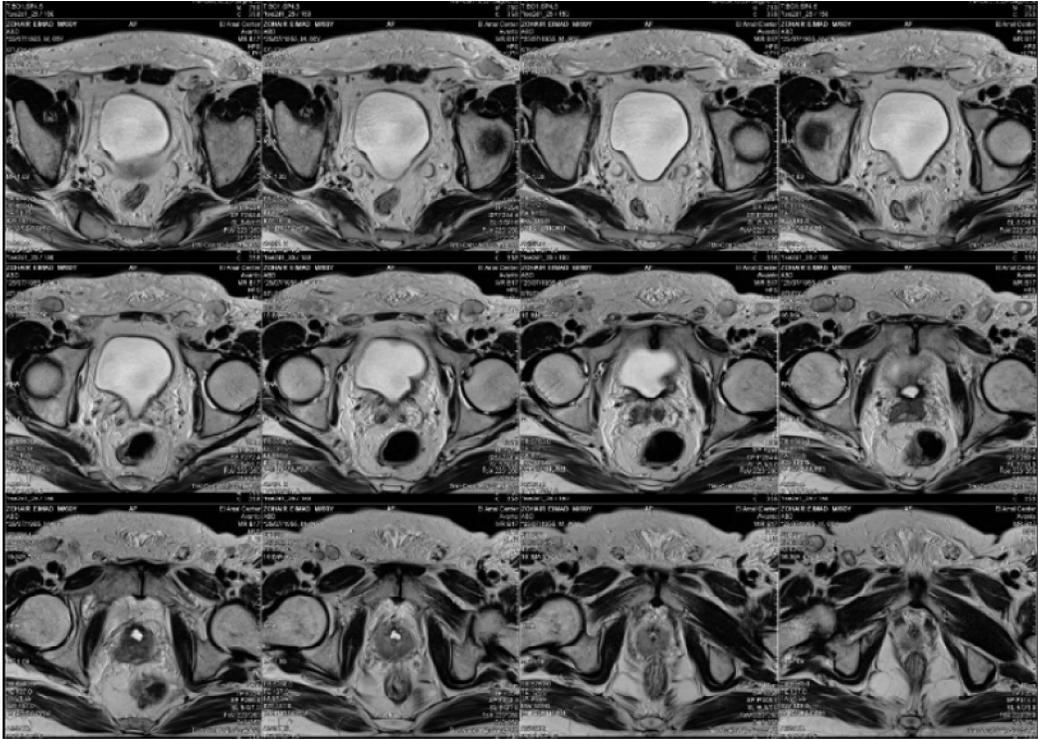


Fig (4) :multiple subcentimetric pelvic lymphadenopathy

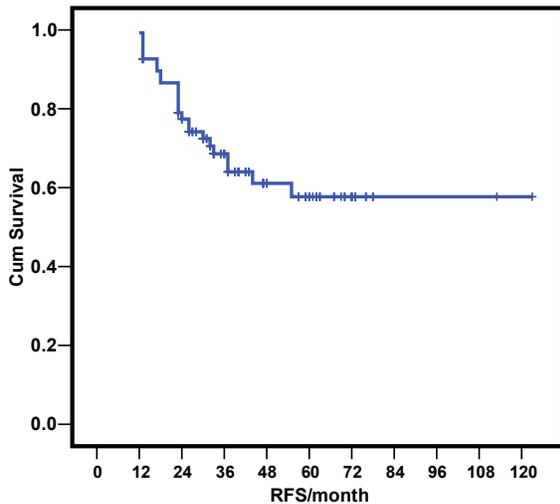


Fig (5), 2- year, 3- year and 5-year RFS rates in the entire study population of 204 patients were, 78. 9%, 68. 6% and 57. 7%, respectively, whereas the 2-year, 3-year and 5-year CSS rates were 80. 3%, 71. 9and 62. 4%, respectively.

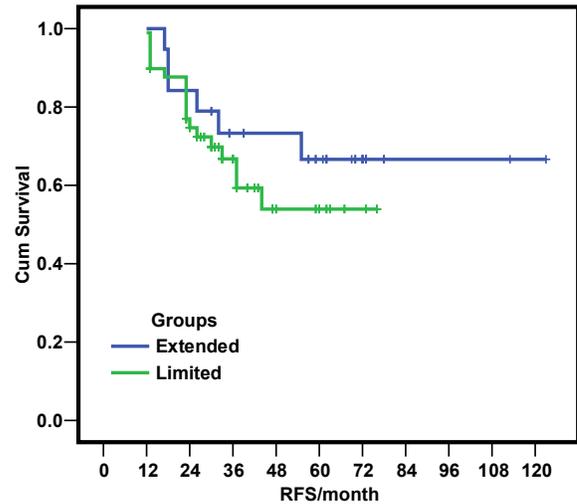


Fig (6). 2- year, 3- year and 5-year RFS rates in the a standard PLND / an extended PLND were 77%,67%,54% / 84%,73%,67% (p= 0. 1153). 2- year, 3- year and 5-year CSS a standard PLND / an extended PLND were 78%,69%,59%,/85%,75%,70% (p=0. 1324)

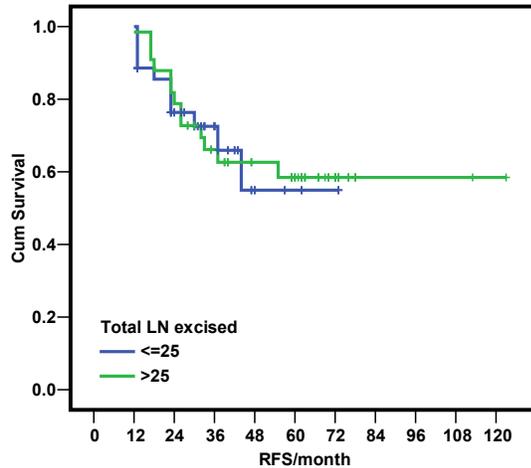


Fig (7) the 5-year recurrence-free survival rates RFS in the patients had  $\leq 25$  lymph nodes, / patients had  $> 25$  lymph nodes Excised 55%, 58% respectively ( $p = 0.9099$ )

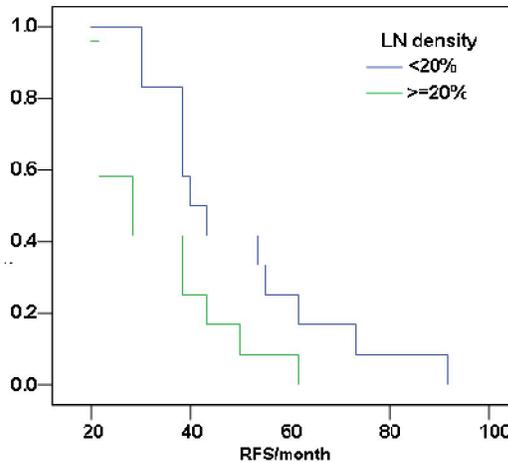


Fig (8) the 5-year recurrence-free survival rates in the Lymph node density In patients  $\leq 25$  20% was 36% and 17% when Lymph node density  $> 20\%$  with significant ( $p = 0.0001$ ). The 5-year survival in patients with a lymph node density in patients  $\leq 25$  20 % was 39% and 18% for patients with Lymph node density  $> 20\%$  significant  $p$  value (0.0001)

#### 4. Discussion

Extensive lymphadenectomy increases the operating time and theoretically may increase the risk of hemorrhage and lymphocyte formation, however many authors<sup>13, 21</sup> show no significant increase in morbidity with this procedure, it is recorded that there is increase in operative duration by 63 (30-63) minutes.<sup>8, 16, 22</sup> We are in agreement with this as in our study; the increase in operative time between the 2 groups is estimated to be 35 minutes, Also our results shows no significant difference among the

perioperative mortality, early complications or the need for blood transfusion. In this we are in agreement with results of the former studies.<sup>8, 16, 22</sup>

Although dissection of the retroperitoneum between the aortic and iliac bifurcations may disrupt regional sympathetic nerve without functional implications. In former studies<sup>5, 7, 9, 12, 23</sup> a few percentage ranging from 1-2% will develop lymphoceles or lymphoedema. In our study we did not encounter lymphocele or lymphedema, this may be attributed to following the most recent improvements surgical technique and improvement in postoperative care resulting in lowering perioperative mortality.

Conventional CT and MR imaging are limited by their ability to detect metastases in normal or minimally enlarged lymph nodes. Relying on size as a sole criterion for the diagnosis of nodal metastases represent a fundamental problem.<sup>24</sup>

Prenzel *et al.*<sup>25</sup> Relied on the premise that malignant lymph nodes were larger than benign ones.

In our study we tried to calculate a cut-off point for each lymph node group as we agree with the fact that depending on size criteria is difficult as there is wide variation in size of non- metastatic lymph nodes, which can substantially overlap with the size of metastatic nodes.<sup>24</sup>

The number of lymph nodes assessed pathologically depends upon several factors including: (1) the boundaries of the lymph node dissection (extended verses standard), Poulsen *et al.* reported that extending the boundaries of the PLND increased the mean number of retrieved lymph nodes from 14 in a standard PLND 25 when the dissection was extended to the bifurcation of the aorta Skinner's group, who reported that extending the dissection to the inferior mesenteric artery increased the median lymph node count from 30 to 56 nodes from (8. 5 to 36. 5) (10 to 53) (13 to 72) (22 to 12) nodes.<sup>4, 6-8, 12, 23</sup> (2) the pathologist's diligence in searching and preparing the lymph nodes for histopathological evaluation, and (3) It is reported that whether the lymph nodes are submitted as separate packets or en bloc influences total lymph node count. but not the percentage of patients with lymph node metastases from 21 to 40 or 3-fold<sup>2, 26</sup>, Groups have reported median lymph node counts of 23, 25, and 39 when the dissection is confined to an ELN with packaged nodal submission.<sup>26</sup> in our study the slandered group sent in six packets or in en bloc according to the surgeon but **the** extended group which performed by one surgical team sent in a ten packs. **the mean total lymph nodes in extended PLD with ten packed is 37 (24-53) nodes compared to 21 (8-39) a standard PLND ( $p = 0.001$ ).**

There is a controversy debate about the minimum number of lymph nodes needs to be removed at radical cystectomy to optimize oncologic outcome and accuracy of nodal staging and removing 16 lymph nodes was necessary to detect nodal metastases and was also associated with improved disease-free and cancer-specific survival Similarly Herr *et al.* confirmed an improved survival for not only patients with nodal metastases but also patients without nodal metastases when a minimum of nine lymph nodes, A minimum lymph node counts of 5, 10,14, and 20- has been recommended, extensive lymph node dissections may have a direct therapeutic effect, either by removing micrometastatic disease or by sorting patients into their true pathologic stage. The former may result in lower recurrence rates, whereas the latter will better identify those in need of potentially curative adjuvant therapy. <sup>27, 28</sup>. another study, RC with 'extended' LND with the removal of more than 16 lymph nodes resulted in a 22% five-year survival advantage. Herr and colleagues, similarly, found that patients who had a more extensive PLND had improved overall survival in our study a minimum lymph node counts was 8 nodes a standard PLND and 24 nodes an extended PLND.

progression-free survival and overall survival have been correlated with the number of nodes removed better prognosis after removal of more LNs. <sup>15</sup>. node count is not an independent predictor of survival,<sup>4, 9, 22, 23</sup>. the number of retrieved nodes correlated with cancer-specific survival and that a significant survival advantage was noted when  $\geq 16$  nodes were removed: if more than 16 lymph nodes were removed, the 5-year recurrence-free survival increased from 63% to 85% in organ-confined tumors, <sup>6</sup>survival rate for patients with !10 lymph nodes removed was significantly lower compared to patients with 1 10 lymph nodes removed; 44 vs. 61%, respectively<sup>8</sup>. in our study The 5-year recurrence-free survival rates in  $\leq 25$  lymph nodes, was 55% and 58% for  $> 25$  lymph nodes Excised ( $p= 0. 9099$ ). The 5-year cancer specific survival rates in  $\leq 25$  lymph nodes was 58% and was 67% in  $> 25$  lymph nodes Excised ( $p= 0. 5130$ ) this finding did not reach statistical significance

Lymph node density is superior to TNM nodal status in predicting disease specific survival becoming accepted as prognostic variables. <sup>2, 3, 26</sup>. Stein *et al.* reported a lymph node density of less than 20% was associated with a better recurrence-free survival (5- and 10-year recurrence-free survival of 44 and 43%, respectively) when compared with a lymph node density of greater than 20% (5- and 10-year recurrence-free survival of 17%). <sup>26</sup>. The 5-year survival in patients with a lymph node density of less than 20 was 64%, significantly higher than the 8% for

the same pathologic group of patients with a lymph node density greater than 20% . <sup>3</sup>Patients with a lymph node density of 20% or less, demonstrated a 43% 10-year recurrence- free survival compared to only a 17% survival at 10years, when greater than 20%,<sup>16, 26</sup>. in our study The 5-year recurrence-free survival rates in the Lymph node density equal or less than 20% was 36% and 17% when Lymph node density more than 20% with significant ( $p = 0. 0001$ ). The 5-year survival in patients with a lymph node density equal or less than 20 % was 39% and 18% for 36 patients with Lymph node density more than 20% significant  $p$  value (0. 0001).

Overall analysis showed a significantly better RFS rate in patients who had undergone extended PLND than in those who had undergone non-ePLND,stan Poulsen *et al.* and found a statistically significant was 44% compared with 61%<sup>29</sup>Poulsen *et al.* demonstrated that an extended PLND is beneficial in patients with organ-confined, lymph node-negative disease. The 5-yrrecurrence-free survival rate was 90% in extended PLND group versus 71% in the standard PLND group ( $p < 0. 02$ ). Moreover, extended PLND reduced the rate of pelvic and distant metastases. <sup>21</sup> lymph node- negative patients for a significant increase in 5-yr tumor free survival from 63% to 85% in patients with tumor confined to the bladder wall Leissner *et al.* reviewed their experience with 447 patients 5-year recurrence- free survival rate was 62% for the extended PLND group and 56% for the limited PLND group; this difference did not achieve statistical significance. <sup>26</sup> patients with 90% 5-year RFS compared to only 71% when a standard LND was performed. 24 (62 vs. 56% limited dissection) (85 vs. 64%) compared recurrence pattern and survival in standard PLND and extended PLND<sup>5</sup>. in our study 5-year recurrence-free survival rates in the a standard PLND / an extended PLND were 54% compared to,67% this difference did not achieve statistical significance ( $p= 0. 1153$ )

Leissner *et al.* showed that extended PLND significantly improved the prognosis of patients with invasive bladder cancer in both node-negative and node-positive patients when a greater number of lymph nodes was resected. <sup>21</sup> The 5-year overall and recurrence-free survival rates in the entire study population of 336 patients were 68% and 69%, respectively<sup>30, 31</sup>. . 2- year and 5-year RFS rates were 39. 6% and 22. 3%, respectively, whereas the 2-year and 5-year DSS rates were 58. 1% and 33. 8%, respectively. <sup>32</sup> The 5-year disease-specific survival and recurrence-free survival for the 46 patients overall were 41. 3 and 32. 2%, respectively. <sup>28</sup>

In our study, 2- year, 3- year and 5-year RFS rates in the entire study population of 204 patients were, 78. 9%,68. 6% and 57. 7%, respectively,

whereas the 2-year, 3-year and 5-year DSS rates were 80.3%, 71.9% and 62.4%, respectively. We had comparable results with good RFS and CSS mostly our patient had lower pathological stage confined to bladder wall

Recognizing the complex nature of the lymphatic drainage of the bladder, lymphatic crossover, lack of a sentinel lymph node, results in an unpredictable distribution of lymph node metastases and the possibility of skip metastasis (negative pelvic nodes, positive pelvic proximal common iliac packets (above the ureter) and in the para-aortic and paracaval packets (above the aortic bifurcation). This is extremely low. Varian *et al.* reported that 24.4% had lymph node involvement at places other than the 'standard' template and 9% had disease above the common iliac bifurcation while 'skip metastasis' above the common iliac bifurcation was reported in only one patient,<sup>8,9,14,26,33</sup>, in our study a 'skip metastasis' occurred in 1 patient of extended PLND with positive lymph nodes at para aortic nodes without involvement of the more distal pelvic lymphatics.

Our study had several limitations. The number of patients in this study was small, which imposed limitations on statistical power. This was a retrospective analysis, which created the potential for selection bias. Further large, prospective investigations and long-term follow-up are required to evaluate the definite conclusions.

### Conclusions:

Extended LND proximally to the level of the inferior mesenteric artery. is recommended yields higher number of lymph nodes more accurate staging low skip metastases improves the recurrence-free survival rate and cancer specific survival to patients with both node-positive and node-negative disease without increasing morbidity or perioperative mortality compared to limited LND. for bladder cancer

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