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Extended Lymphadenectomy to the Lower Paraortic Nodes During Radical Cystectomy

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ABSTRACT

Purpose: Evaluation of the diagnostic, prognostic and possible therapeutic role of extended lymphadenectomy to lower para-aortic area in operable bladder cancer patients.

Patients and Methods: One hundred and nine patients were subjected to the procedure in the National Cancer Institute, Cairo University, and in Minea Oncology Center, Ministry of Health by the same group of surgeons, during the period from September 2000 to March 2003. The lymph nodes dissected were labeled to the following groups: perivesical, lymph node of Cloquet, external iliac, internal iliac and obturator, common iliac and paraortic groups both right and left. These nodes were subjected with the primary tumor to serial sectioning for histopathologic examination. Preoperatively, all patients were subjected to routine laboratory investigations. In addition to cystoscopy, biopsy and histopathologic examination, bone scan, chest X-Ray and computerized tomography with I.V. contrast examination for the abdomen and pelvis were done for clinical staging of the disease.

Results: 34.4% of the node positive patients have been found to harbor the disease in the para-aortic lymph nodes above the common iliac bifurcation. Obturator, external iliac, internal iliac, para-aortic, common iliac, perivesical and lymph node of Cloquet are the higher incidence groups of positive lymph nodes sequentially. The clinical and C.T. staging are inaccurate methods of diagnosis due to high overall error in up to 70.6% of patients. There is no higher incidence of morbidity, mortality, operative time or intraoperative blood loss related to the addition of lower para-aortic dissection to the routine radical cystectomy.

Conclusion: Extension of lymphadenectomy to include the lower para-aortic area in addition to the standard pelvic lymphadenectomy during radical cystectomy for bladder cancer is a more accurate technique for diagnosis and staging of bladder cancer patients and it may help in determining the benefit of adjuvant chemotherapy ± radiotherapy. By itself, it gives a better recurrence-free survival rate without adding higher morbidity or mortality than the standard pelvic lymphadenectomy.

Key Words: *Bladder cancer - Lymphadenectomy - Para-aortic node dissection.*

INTRODUCTION

Radical cystoprostatectomy including bilateral pelvic lymph node dissection (P.L.N.D) is the standard treatment for muscle invasive bladder cancer [1]. El Sebai showed that bilharziasis presents several favorable features that affected the behaviour of the vesical tumor and its spread to pelvic nodes. This may represent a distinct clinicopathological entity that differs from the Western World [1]. The incidence of pelvic lymph node metastases in carcinoma of the bilharzial bladder was found to be between 12 and 34.3% in reports of different Egyptian investigators [2-6].

According to Whitmore and Smith, obturator and the external iliac nodes appear to be of greatest importance because of their frequency of involvement by metastatic cancer followed by the common iliac, the hypogastric and the perivesical nodes [7].

William et al., concluded that the best chance of survival in the presence of lymph node involvement at the time of radical cystectomy is probably in those patients with micrometastatic lesions in macroscopically normal appearing lymph nodes along the hypogastric arteries, provided these nodes are meticulously removed [8].

In the Egyptian series, the obturator group of lymph nodes was the most frequently involved group. El Sebai reported in his series that the obturator group of lymph nodes was the most commonly involved group by metastatic deposits in bilharzial bladder cancer [1]. Imaging technique such as C.T., M.R.I., and/or ultrasonography are useful in determining local

stage and the presence of distant metastasis but not equally reliable in identifying nodal involvement, especially when lymph nodes involvement is small or microscopic [9]. In fact, pelvic lymphadenectomy provides an accurate method for staging as a significant number of patients with clinically negative nodes have microscopic metastasis found on histopathologic examination (18%), and in turn an effective adjuvant therapy for those patients will be decided [10,11].

The addition of adjuvant local measures either in the form of preoperative or postoperative irradiation has led to better local control and, subsequently, a better disease-free survival [12]. The improvement in survival rate of these patients treated with adjuvant radiotherapy has allowed a greater number of distant metastasis to appear which occurred in 27% of patients, and it was reported that 70% of these metastases were in the bony pelvis, 10% in the lung, and 8%, 6%, and 6% in the lymph nodes, liver, and brain respectively [13]. Between January 1990 and March 1993, Asgar and his group were performing pelvic lymph node dissection bounded proximally by bifurcation of the common iliac vessels, laterally by genitofemoral nerve, distally by the circumflex iliac vein and Cloquet's lymph node and posteriorly by the internal iliac vessels, including obturator fossa. Between March 1993 and September 1997, he justified the extended lymphadenectomy to include the bifurcation of the aorta based on better recurrence-free survival rate for patients that underwent extended pelvic lymphadenectomy including para-aortic lymph nodes in comparison to patients that underwent only pelvic lymphadenectomy without adding to the morbidity or mortality of the procedure [14].

This extended procedure was also described by Skinner and Lieskovsky and by Steven [15,16]. The results of these studies supported the concept of better recurrence-free survival for those patients that underwent extended lymphadenectomy in comparison to the standard pelvic lymphadenectomy for tumors confined to the bladder wall and the finding of significantly improved survival for the entire patient population with tumors confined to the bladder wall and not only for the subpopulation without nodal improvement. This disputes the supposition that stage migration contributes to survival advantage and this observation supports the assertion that extensive lymphadenectomy should be included when performing radical cystectomy for bladder cancer [14].

PATIENTS AND METHODS

One hundred and nine patients were subjected to radical cystectomy with extended lymphadenectomy from September 2000 to March 2003 (including bilateral pelvic lymph nodes dissection up to the lower para-aortic level). The study included 93 male patients (subjected to radical cystectomy and extended lymphadenectomy and 16 female patients (subjected to anterior pelvic excentration and extended lymphadenectomy).

Cases were done by the same group of surgeons (dedicated to the surgical department of the National Cancer Institute Cairo University) and in EL Minea Oncology Center, Ministry of Health.

All patients were evaluated clinically preoperatively by personal history, clinical examination in addition to cystoscopy and biopsy for pathologic study. Chest X-Ray, Computerized abdomino-pelvic tomography, bone scan and routine laboratory assessment.

Technique:

1- Starting by midline exploratory incision, the parietal peritoneum is reflected from the pelvic wall and pelvic lymph nodes dissection was followed in a cephalad direction from the node of Cloquet distally, genitofemoral nerve laterally, skeletonizing the external internal iliac vessels and obturator nerves. Medially, devascularization of the bladder was done and proximally up to lower paraaortic region (the area immediately below the aortic bifurcation and up to about 4-6 cm above on both sides).

2- Each group of lymph nodes was labelled either right or left, namely lymph node of Cloquet, external iliac, internal iliac, obturator, common iliac and the lower paraaortic groups.

3- After extended lymphadenectomy was completed on both sides, cystectomy or anterior pelvic excenteration was completed as well as the suitable urinary diversion adapted for the patient.

4- Blood loss was calculated, good drainage and closure of the abdomen was done as usual.

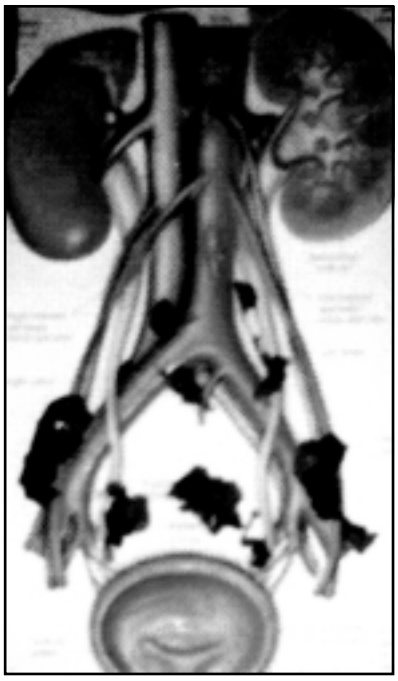

Fig. (1): Right and left regional and Juxtaregional excised lymph nodes, distributed on an illustrating diagram of the urinary system.

The specimen was subjected to detailed histopathologic study to comment on both a) gross, and b) microscopic examination as follows:

1- *Gross:* Tumor site, size, gross picture, involvement of adjacent organs (ureters, seminal vesicles, prostate, uterus, cervix, vagina, ovaries), number and size of the dissected groups of lymph nodes, right and left cloquet, external iliac, internal iliac, obturator, common iliac and lower para-aortic groups.

2- *Microscopic:* Tumor histopathologic type (squamous, transitional, adenocarcinoma or undifferentiated carcinoma), grade, depth of infiltration with bladder wall, existence of bilharziasis, extravesical extension (to ureters, cervix, seminal vesicles, prostate, uterus, cervix, vagina, ovaries), number of the lymph nodes involved in each group and lymph node status (capsular invasion, follicular hyperplasia, fat degeneration).

Statistical Analysis:

It was done according to Ingelfinger et al. (1994), and Knapp and Miller (1992).

Statistical Tests:

Descriptive statistics was presented as means, standard deviations, median and number and percentage (frequency distributions). Analytical tests used included impaired student t test (two sided) for comparing two groups. Analysis of variance (F test) was used for comparing more than 2 groups and post hoc test for comparing each two groups.

Significance Level:

Significance level of 0.05 and 0.01 was used throughout all statistical tests within this study.

Tabulation was also done according to Knapp and Miller (1992).

RESULTS

The time needed to extend the procedure of lymphadenectomy to the lower para-aortic area in our series was 10-20 minutes with a mean of 5.7 minutes.

Table (1): Time needed to extend dissection to the lower para-aortic area.

	N	Minimum	Maximum	Mean	Standard Deviation
Time (Min)	109	10.00	20.00	15.00	2.0461
Valid (N) Listwise	109				

It was obvious that there was a minimum blood loss due to extending the lymph node dissection. The minimum blood loss for all the operation was 600 cc and maximum was 2000 cc. There was no relation between the extension of lymphadenectomy to lower para-aortic area and morbidity or mortality (0%).

The histopathologic typing of the 109 patients included 61 cases of squamous cell carcinoma (55.9%); 37 patients with transitional cell carcinoma (33.9%), 10 patients with adenocarcinoma (9.1%), and one patient had leiomyosarcoma of the bladder (0.9%).

There were 96 patients with bilharzial and 13 patients had non bilharzial bladder cancer distributed among this histopathologic group, (Table 2).

Table (2): Histopathologic types in bliharzial and non bilharzial bladder cancer.

Histopathological types	Bilharzial		Non-bilharzial	
	No.	%	No.	%
Squamous cell ca.	55	50.4	6	5.5
Transitional cell ca.	31	28.4	6	5.5
Adenocarcinoma	10	9.2	—	—
Leiomyosarcoma	—	—	1	0.9
Total	96	100%	13	100%

The distribution of node positive and node negative patients according to the histopathologic types is shown in table (3).

Table (3): Distribution of node positive and node negative disease according to histopathological typing.

Histopathological types	N0		N1	
	No.	%	No.	%
Squamous cell ca.	51	46.8	10	9.2
Transitional cell ca.	21	19.2	16	14.9
Adenocarcinoma	5	4.5	5	4.5
Leiomyosarcoma	1	0.9	00	00.00
Total	78	7 1.4%	31	28.6%

Chi^2 *p*-value

Grade II tumors represented the majority of patients in our study (109 patients). 71 patients (65%) were grade II. Grade I patients were 19 (17%) and grade III patients were 18 (16%) and grade IV was seen in one patient (0.9%). There was a highly significant correlation (*p*-value: 0.001) between tumor grade and number of positive lymph nodes (Table 4).

Table (4): Distribution of node positive and node negative patients according to histopathological staging.

Grade	N0		N1	
	No.	%	No.	%
I	19	24.35	0	00.00
II	50	64.10	21	67.74
III	8	10.25	10	32.25
IV	1	1.82	0	00.00

Chi^2 16.26 *p*-value 0.001** ** Highly significant

Among 2084 lymph nodes which were dissected by extended lymphadenectomy procedure, 114 nodes were positive, distributed in different lymph node sites as shown in Table (5).

Table (5): Distribution of the 114 positive lymph nodes.

Nodal site	No. of nodes involved			Percentage
	Right	Left	Total	
Obturator	18	12	30	26
External iliac	11	12	23	20
Internal iliac	8	8	16	14.9
Para aortic	9	6	15	13
Perivesical	—	—	15	13
Common iliac	8	5	13	11.4
Lymph node of Cloquet	2	—	2	1.7
Total	56	43	114	100

In our series, out of 109 patients, 31 proved to have positive lymph nodes (28.4%). There were 9 patients (29%) with one positive node below the common iliac bifurcation (N1), 8 patients (25.8%) with two or more positive nodes below common iliac bifurcation (N2), 4 patients (12.9%) with positive nodes bilaterally (N3) and 10 patients (32%) with positive lymph nodes above the common iliac bifurcation (N4) (Table 6).

Table (6): Distribution of node positive patients according to lymph nodes position in relation to the common iliac bifurcation.

Distribution	No.	%
N1	9	29.03
N2	8	25.80
N3	4	12.90
N4	10	32.25
Total	31	100

In our series, the overall error in clinical staging compared to the pathologic status of the disease was 70.6% with a tendency for overestimating the pathologic extent of the disease.

There were 66 overstaged cases (60.5%), and 11 cases were understaged (10.09%). The clinical staging was correct in 32 cases (29.35%).

Regarding clinical staging by computerized tomography, there was an overall error of 70.6%, forty cases were overstaged, and thirty seven

cases were understaged. Computerized tomography was correct in 32 cases (29.3%) out of 109.

DISCUSSION

Limited pelvic node dissection with the superior boundary represented by the bifurcation of the common iliac artery has been adopted based on the failure to observe nodal metastasis above this level, but Skinner and Asgar reported that extensive lymphadenectomy should be included when performing cystectomy for bladder cancer based on the fact that a more comprehensive dissection results in excision of a significantly greater number of lymph nodes, which presumably increases the sensitivity in detecting lymph node metastasis [11,14,15].

El-Sebai reported that bilharziasis affects the pathologic features and behavior of bladder tumors leading to a lower incidence of nodal metastasis in comparison to that experienced in the Western world, but in our series, although 96 (88%) proved to have bilharziasis, and 13 patients (12%) did not have bilharziasis, both groups had the potential to have lymph node metastasis (27 patients in the bilharzial group and 4 in the non bilharzial group) [1].

It was obvious in our study that the grade of the tumor depth of infiltration in the bladder wall and the tumor size, are the most important factors that were significant in determining the incidence of lymph node metastasis. The higher the tumor grade (not the histopathologic type), the more the penetration in the bladder wall, the bigger the size of the tumor, the more the incidence of lymph node metastasis. This correlated with other studies.

In our study, the higher the grade, the higher the incidence of lymph nodes metastasis (0%) for grade I, 29.5% for grade II, and 95.5 for grade III. In a study by El Bolkainy, the incidence of lymph node metastasis was 8.7% for grade I, 16.8% for grade II, and 30.8% for grade III tumors [17]. In our study, the incidence of lymph node metastasis increased with bladder wall penetration it was 0% for Tis, 3.2% for T1, 9.7% for T2a, 35.5% for T2b, 6.5% for T3a, 29% for T3b, 9.6% for T4a, and 6.5% for T4b. In the Whitmore and Smith study, it was 2% for Pis, 1% for P1, 8% for P2, 47% for P3, and 42% for P4 stage [7].

Regarding the correlation between tumor size and incidence of lymph node metastasis, it was statistically significant ($p = 0.014$). The mean size was 5.75±2.2, the minimum size was 1 cm and maximum size was 16 cm.

During lymph node dissection in radical cystectomy, the anatomic distribution of lymph node metastasis is important as there are certain groups which are more prone to harbor metastasis more than others. The obturator group (part of the internal iliac groups) came first, followed by external iliac group, then the distal common iliac group [2,7].

In our study, the incidence of para-aortic lymph node metastasis came next to the external iliac lymph node metastasis and before the common iliac lymph node metastasis representing 13% of the positive lymph node site, equalizing the perivesical group of lymph nodes and this reflected a figure of 34.4% of positive lymph node patients above the common iliac bifurcation.

In our study, there was one case among 31 node positive patents (3.2%) with a skip lesion, where the lower para-aortic nodes were positive without common iliac nodal metastasis. In this case there was one positive right para-aortic node, while the right common iliac nodes were negative on the same side the perivesical, the obturator, and internal iliac nodes were positive. On the left side there were positive external iliac and obturator nodes.

This skip lesion could be explained by the report of Shvetson where he found lymphatic connections between the external iliac lymph nodes and aortic and lumbar nodes of the opposite side in 3% of cases [18].

Doi et al., reported that the accuracy of preoperative diagnosis of lymph nodes metastasis is insufficient [19].

Similar results to our study were presented in the Annual cancer conference of the Egyptian cancer society which was held in collaboration with Wayane state university, Detroit Medical Center and Mansoura urology and Nephrology center from 8-10 January 2003. The department presented 150 (118 males, 32 females) patients with extended radical cystectomy with positive lymph nodes in 39 cases (26%) [20].

Obturator nodes were involved in 25%, of the total No. of the positive lymph nodes, internal iliac group in 20%, common iliac group in 24%, external iliac group in 13%, para aortic nodes in 12%, inter-common iliac lymph nodes in 6%.

The computerized tomography findings for evaluation of lymph nodes preoperatively in the area between common iliac and para-aortic area was inaccurate with low sensitivity and specificity. McCarthy reported that CT and MRI are no longer used routinely for preoperative evaluation of pelvic lymph nodes because of unacceptable false-negative and positive results **[21-23]**.

The same was noted in our study where the CT error was 70.6% either by overstaging of cases in 52% or by understaging of cases in 48%. Also, the overall error of the clinical staging compared to the pathological findings was 70%. With overstaging in 60.5% of cases and understaging of 10% of cases as shown in (Tables 7,8).

Table (7): The correlation between clinical and pathological staging.

	0		2		3		4	
	No.	%	No.	%	No.	%	No.	%
Tis	0	00	0	00.0	1	1.28	0	00.00
T1	0	00	3	25.0	3	3.84	0	00.00
T2a	1	00	0	00.0	16	20.78	1	4.55
T2b	0	00	3	50.0	27	35.06	6	27.27
3a	0	00	2	25.0	2	2.60	1	4.55
3b	0	00	0	00.0	21	24.68	8	31.82
4a	0	00	0	00.0	6	10.39	3	18.18
4b	0	00	0	00.0	2	2.60	3	13.64

Chi^2 42.11 *p*-value 0.004** ** Highly significant

Table (8): Correlation between pathological and computerized tomography staging.

T	T2b		T3a		T4a		T3b		T4b		T0	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Tis	1	1.88	0	00	1	3.44	0	00.00	0	00.00	0	00.00
T1	5	9.43	0	00	0	00.00	0	00.00	0	00.00	0	00.00
2b	8	7.54	1	50	0	00.00	0	00.00	0	00.00	0	00.00
2a	19	35.84	0	00	11	37.93	3	18.75	3	37.50	0	00.00
T3a	4	15.09	1	50	4	13.79	5	31.25	0	00.00	0	00.00
4b	13	1.88	0	00	1	3.44	3	18.75	0	00.00	0	00.00
3b	2	24.52	0	00	7	24.13	5	31.25	4	50.00	0	00.00
4a	2	3.77	0	00	5	17.24	0	00.00	1	12.50	1	10.00

Chi^2 47.12 *p*-value 0.083

It is clear now that extended lymphadenectomy has both diagnostic and therapeutic role in determining patients who harbor the disease in the lymph nodes beyond the classic level of P.L.N.D and who will need adjuvant therapy.

These patients will benefit from being locoregionally free of the disease as proved by the study of Asgar and Thomas who reported and explained the survival advantage associated with extended lymphadenectomy by removal of tissue harboring microscopic nodal metastasis **[14]**.

Extending the level of dissection of lymph nodes to the lower para-aortic area was not associated with higher morbidity, mortality, or more time consumption. This was also in agreement with Asgar and Thomas with the only exception of one mortality related to the procedure of extension of lymphadenectomy being (0.5%) in their series, which was due to intraoperative bleeding during dissection in the para-aortic area **[14]**.

Conclusion:

Extension of lymphadenectomy to the lower para-aortic area has both diagnostic and therapeutic benefit by accurately defining a group of patients who might benefit from adjuvant chemotherapy ± radiotherapy and will have a higher incidence of recurrence-free survival rate than other groups of patients who had a standard pelvic lymphadenectomy for bladder cancer.

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