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Lymph Node Size: Does It Reflect the Status of Tumor Metastasis in Gynecologic Malignancy ?

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ABSTRACT

Objective To study whether the lymph node size is a reliable indicator in determining the presence of gynecologic cancer metastasis.

Study design Diagnostic study.

Setting Gynecologic oncology unit, Department of Obstetrics and Gynecology, Department of Pathology, Bangkok Metropolitan Administration Medical College and Vajira Hospital.

Subjects Pathological specimens from four hundred and nine gynecologic cancer patients who had undergone various types of pelvic surgery that included lymph nodes resection between January 1994 and December 1999.

Method All sections of lymph nodes were reviewed and measured in two dimensions. The size of nodes were serially leveled and studied pathologically to determine the sensitivity and specificity in determining cancer metastasis.

Main outcome measures The numbers of positive and negative nodes with their sizes in two dimensions, the sensitivity and specificity of lymph nodes size in determining cancer metastasis.

Results Out of 7,260 total nodes obtained, 265 nodes (3.7%) were found to be positive for metastatic cancer. Among these positive nodes, 17 nodes (6.4 %) had nodal maximal axis of ≤ 3 mm while 141 nodes (53.2%), 81 nodes (30.6%) and 26 nodes (9.8%) had nodal maximal axis of > 3 - 10 mm, > 10 - 20 mm and > 20 mm respectively. More than half (59.6%) of these positive nodes axis were ≤ 10 mm and most (90.2%) were ≤ 20 mm. Based on the widely accepted size 10 mm of node as pathological enlargement, the sensitivity and specificity would be 40% and 81 % respectively.

Conclusion Evaluation of lymph node status by sampling only the enlarged nodes does not represent the true positive incidence of nodal metastasis which in turn leading to inaccurate staging and management. To avoid this kind of misclassification error, a complete lymph nodes dissection is encouraged in all patients undergoing surgical staging.

Key words: Neoplasm metastasis, lymphadenectomy

As we all realize that the presence of metastatic disease in lymph nodes is indicative of systemic dissemination and cases with lymphatic extension relapse more frequently than those without nodal disease.[1] The clinical assessment of the nodal status using lymphangiogram, computed tomography or MRI has been less than satisfactory. Lymphangiogram has been use less frequently because of technical difficulty and considerable false positive and negative rate with low sensitivity about 25-29%.[2,3] Mainly, detection of nodal metastasis with CT scan and MRI are based on size criteria. One cm of nodal size is usually used as the upper limit of normal.[4,5] But this is not for conclusive diagnosis since the small nodes could be positive for tumor metastasis or the enlarged nodes might be due to reactive hyperplasia. These limitations lead these tests to achieve only low sensitivity for detection of tumor metastasis. CT scan, in diagnosis of lymph nodes metastasis, has sensitivity of only 18-60% with specificity about 79-95% while MRI has similar values with sensitivity and specificity about 20-68% and 78-91% respectively.[2-6]

Nowadays, lymphadenectomy is included in most of the gynecologic oncology surgery either as a part of complete and accurate surgical staging or treatment. The procedure may range from "complete dissection" together with radical hysterectomy for patients with cervical cancer or only "sampling or selective" in uterine and ovarian cancer. However, in uterine and ovarian cancer, some surgeons still insist for a complete procedure because they realize about the risk of undetected extrauterine or retroperitoneal metastasis in omitting systemically sampling pelvic and paraaortic nodes.[7-9] Moreover, this particular process has been found not to increase morbidity and mortality significantly.[10]

For those who select to do only "the sampling", there is a question of how to sample or select these nodes. Some surgeons just feel fine to biopsy only the palpable nodes.[11] But the fact is that these lymph nodes are one of the retroperitoneal structures lying in the fat pads thus they would not readily or easily be accessed for evaluation by palpation. Another fact is that the metastatic lesion can be micrometastasis (less than 2 mm in maximal dimension) in the normal size node which could be diagnosed only by histologic study.[8,9] On the other hand, a lymh node enlargement can be due to either metastatic cancer lesion or inflammatory process or even benign reactive hyperplasia per se.[12] These even add more controversies to the questions previously mentioned.

The aim of this study is to evaluate the association between the size of lymph nodes and the presence of cancer metastasis by comparing the size of positive and negative nodes. This will help either supporting[11] or rejecting[8,9] the concept of sampling lymphadenectomy. We also try to determine the size of node which yields the most appropiate sensitivity and specificity for screening and to assess pathological if we could utilize it for effective nodal selection.

Materials and methods

This study included specimens from 409 gynecologic cancer patients (either cervical, uterine or ovarian in origin) who underwent surgical procedure at the Department of Obstetrics and Gynecology, Bangkok Metropolitan Administration Medical College and Vajira hospital between January 1994 to December 1999. All patients underwent either primary or secondary pelvic surgery with lymph nodes resection.

Routinely in the Department of Pathology, the fat pads containing lymph nodes were separately fixed and submitted in individual groups. All identified discrete nodal tissue or firm area (possible lymph node) were dissected. The grossly potential nodes were measured at their greatest dimension after fixation and before processing. Then tissues were embedded in paraffin and processed as serial sections of five microtomes apart for at least one, and usually two to three sections for each tissue block.

All slides were reviewed and studied by one pathologist who measured sections of all nodes in two dimensions from the glass slides in absolute number of millimeter unit (mm). Lymph nodes of size larger than five mm were measured by a standard ruler. Nodal

size of less than five mm was measured by a Vernier scale, also in absolute number. Nodes of striking enlargement that could not be pasted totally on a slide were referred for a gross measurement. Then all those slides which had been already measured were histologically examined for the presence of any tumor metastasis and serially recorded. The negative but suspicious nodes were further stepped for an additional study. Then the results were referred to the official pathological reports. If there was any disagreement in diagnosis of nodal metastasis between the study and the previous reports, the slides were conferred to another senior pathologist who would make the final decision. Demographic datas were obtained from the patients files.

Data was analysed by parametric and nonparametric statistics, using SPSS 7.5. Desciptive statistics were used for demographic baseline data and summarized as mean with standard deviation (SD), or median with range. Continuous variables were examined for normal distribution(Kolmogorov-Smirnov test) before using parametric statistics. Differences between continuous variables were evaluated with unpaired t-test for variables that were normally distributed and the Mann-Whitney U test for variables that were not normally distributed. Categorical variables were evaluated with Chi squared test or Fisher's exact test as appropiate. The primary outcome was considered significant only if $p < 0.05$. The receiver operating characteristic curve (ROC-curve) was plotted between sensitivity and 1-specificity to determine the appropiate cut-off point of lymph node size in correlation with tumor metastasis.

Results

Total number of 7,260 nodes from 409 patients with gynecologic cancer were studied between January 1994 to December 1999. Various types of surgery were performed for 208 cases of cervical cancer such as radical hysterectomy, post radiotherapy hysterectomy or simply node excision and they yielded 3,223 nodes (44.4%). Primary surgical staging were done in 93 cases of uterine cancer with additional one case who had undergone hysterectomy after a radiation treatment with the number of 2,044 nodes (28.1%) obtained. From 107 cases of ovarian cancer, either primary surgical staging or secondary surgical operation were performed which yielded 1,993 nodes (27.5%).

From 208 cases or 3,223 nodes of cervical cancer, the most common histologic type was squamous cell carcinoma. While among 94 cases or 2,044 nodes of uterine cancer and 107 cases or 1,993 nodes of ovarian cancer, the most common type of these two cancers were adenocarcinoma in general. The number and percentage of lymph nodes with various histologic findings of each gynecologic cancer were listed in Table 1.

All nodes yielded were grouped as pelvic (5,570or 76.7 %), subaortic (252or 3.5%), paraaortic (1,304 or 18.0 %) and other miscellaneous groups such as mesenteric, mesocolon and not otherwise specified (134 or 1.8 %). Among the pelvic group, the highest number was from the obturator group and the rest in order of frequency were external iliac, common iliac, internal iliac and pelvic groups with no otherwise specified.

Totally in both positive and negative cases, number of nodes yielded pe case varied from 1-66 nodes depending partly on the type of surgery with the median 18.00 nodes. From 7,260 nodes (409cases), 265 nodes (79cases) were positive for metastatic cancer (3.7%of total nodes). The median number of nodes removed per each metastatic case was 13.0 nodes (range1-45). The median positive nodes per metastatic case was 2.0 nodes (range1-24).

The median positive nodal long axis was 9.0 mm (range1-70) compare to 6.0 mm (range1-88) of the negative nodes while the median positive nodal short axis was 5.0 mm (range1-35) compare to 3.0 mm (range1-17) of the negative nodes. The differences of median in both long and short axis of positive nodes compare to the negative nodes were statistically significant ($p < 0.0001$).

Table 2. showed the number and percentages of positive, negative and total nodes at different long

axis levels.

These numerical datas in turn pointed out that with increment of lymph node size, the frequency of tumoral involvement also increases from 1.0% in nodes ≤ 3 mm, 3.4% in nodes > 3 -10 mm, 6.3% in nodes > 10 -20 mm and up to 21.5 % in nodes > 20 mm. To emphasize on the positive nodes, 59.6% of them had maximal long axis ≤ 10 mm and 90.2% ≤ 20 mm .

As we found that the size of positive nodes were significantly larger than the negative nodes and the frequency of tumoral involvement also increases from small size nodes to larger ones. We try to find the optimal cut off point of nodal size using maximal long axis which can best predict the status of tumor metastasis by plotting the reciever operating characteristic - curve (ROC-curve).[13] The result is shown in Figure 1. We can see that the graph or the ROC-curve was nearly diagonal which means that there is no good cut off point of lymph node size with high sensitivity and acceptable specificity to associate with the status of tumor metastasis. At 10 mm or level of interest, the sensitivity and specificity were 40 and 81% respectively.

Sizes of positive and negative nodes were also studied according to their histology. In conformity with the result of nodal size in total as previously shown in Table2, the positive maximal axis of each histologic type were also larger than the negative ones. We would like to emphasize on the nodal sizes of germ cell tumor and sarcoma that their differences were much more striking than those in total. For common histology as squamous cell carcinoma and adenocarcinoma (in total), we found that the positive median maximal long axis of adenocarcinoma was not that large as that of squamous cell carcinoma (8.5 versus 10.0 mm.). The details of each were shown in Table 3 .

Table 1. Histology of cancer

Histology	CA cervix		CA corpus		CA ovary		Total	
	nodes	%	nodes	%	nodes	%	nodes	%
Squamous cell carcinoma	2,290	71.1	-	-	42	2.1	2,332	32.1
Adenocarcinoma*	899	27.9	1,785	87.3	1,576	79.1	4,260	58.7
Undifferentiated carcinoma	22	0.7	-	-	-	-	22	0.3
Mixed epithelium	12	0.3	-	-	38	1.9	50	0.7
Sarcoma	-	-	259	12.7	15	0.8	274	3.8
Germ cell tumor	-	-	-	-	190	9.7	190	2.6
Others**	-	-	-	-	132	6.7	114	1.8
Total	3,223	100.0	2,044	100.0	1,993	100.0	7,260	100.0

*Adenocarcinoma includes its various subtypes as adenosquamous, mucinous, clear cell, endometrioid, serous carcinoma and not otherwise specified.

**Others include mixed tumor, granulosa cell tumor and carcinoid tumor.

Table 2. Number and percentages of nodes at different long axis levels

Long axis of nodes at different level	Pathology of node				Total nodes and % at different long axis level	
	Negative		Positive			
	nodes	%	nodes	%	nodes	%
≤ 3 mm	1,727	24.7	17	6.4	1,744	24.0
>3 - 10 mm	3,964	56.7	141	53.2	4,105	56.5
>10 - 20 mm	1,209	17.3	81	30.6	1,290	17.8
>20 mm	95	1.3	26	9.8	121	1.7
Total	6,995	100.0	265	100.0	7,260	100.0

Table 3. Sizes of nodes according to their pathological findings

Histology	Positive nodes (n=279)		Negative nodes (n=6981)		P value*
	n	Median (range) long axis (mm)	n	Median (range)long axis (mm)	
Squamous cell carcinoma	47	10.0 (3-70)	2,285	6.0 (1-30)	<0.0001
Adenocarcinoma *	190	8.5 (1-53)	3,908	6.0 (1-88)	<0.0001
Adenosquamous carcinoma	2	9.0 (8-10)	160	6.0 (1-22)	<0.0001
Germ cell tumor	12	20.0 (7-25)	178	6.0 (1-29)	<0.0001
Sarcoma	11	13.0 (6-33)	263	7.0 (1-29)	<0.0001
Others **	3	4.0 (4-16)	201	7.0 (2-24)	<0.0001

* P value < 0.05 is statistical significant by Mann-Whitney U test.

*Adenocarcinoma includes its various subtypes as mucinous, clear cell, endometrioid, serous carcinoma and not otherwise specified.

Others ** include undifferentiated carcinoma, mixed epithelium, granulosa cell tumor and carcinoid tumor.

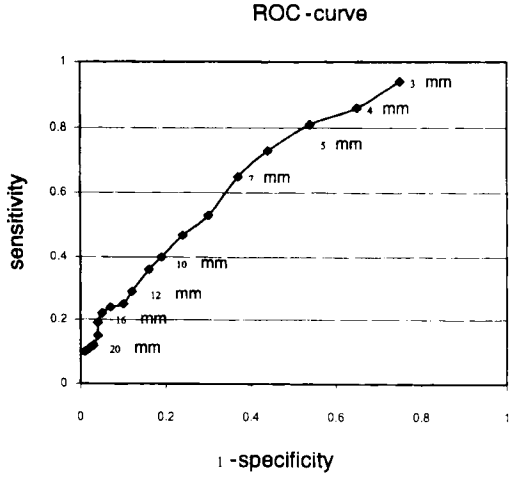

Fig. 1.

Discussion

Lymph node dissection (LND) is now accepted as one of the major part in the current practice in gynecologic malignancy. In cervical cancer, aside from its therapeutic value, it is also one of the most important prognostic factor in correlation with survival.[14] For uterine and ovarian cancer, LND though as a part of surgical staging (FIGO,1988) but it is acceptedly stated as "selective" rather than "systemically" despite of its importance to signify staging, prognosis, survival and plan of treatments.[1,7,15,16] Until recently, this issue was not discussed but rather focused on criteria when to do the node sampling. Particularly in uterine cancer; since the rate of lymph nodes involvement in patient with grade 1 tumor limitted to inner half of myometrium is negligible so lymphadenectomy is usually done in patients with unfavorable prognostic criteria discovered from the operative findings or histologic features.[11,17] Even in these groups of patients who require LN evaluation, the process of the assessment is still not clarified. There is no question for the grossly abnormal nodes which should be removed. But if all nodes look innocent or felt unsuspicious by palpation either by size or consistency, how can we select one/ones?

For uterine cancer, Girardi et al, in 1993[8] and Ayhan et al, in 1995[9] found that up to 37% of positive nodes having size less than 2 mm.[8] and 56.5% of positive nodes having size less than 1 cm. while only 4.5% having size larger than 2 cm.[9] They advocated the role of complete lymphadenectomy rather than mere sampling to obviate understaging error. Chuang et al, in 1994,[11] had applied various techniques to assess retroperitoneal lymph nodes. Though he accepted selective approach (at least 1 para-aortic and 1 right and left pelvic specimen in his study) as accurate enough but as high as 39 % of nodal metastasis were only microscopic.

For ovarian cancer particularly epithelial group, trends have been towards the process of systemic lymphadenectomy. Many have recognized its therapeutic value as well as its role for the exact staging.[15,16,18,19] Spirtos et al, in1994[18] studied the impact of aortic and pelvic lymphadenectomy in cytoreductive surgery in advanced ovarian epithelial cancer. Aside from the main result of positive effect of the procedure on survival, they found 36% of nodal metastasis were microscopic.

Regarding the matter of lymph node size, other organs malignancy reports have also been reviewed. Tiguert et al, in 1999[20] had discovered that pelvic lymph node size was not related with the presence of prostate cancer metastasis. Up to 74% of positive nodes had size less than 1 cm and 26% have size less than 0.5 cm. Monig et al, in 1999,[20] had studied the size of 698 regional lymph nodes in colon cancer. They found that up to 53% of positive nodes had size less than 5 mm. and they concluded that lymph node size was not a reliable indicator of lymph node metastasis in colon cancer.

From our study, the median longitudinal axis of positive nodes was 9.0 mm. which was statistically different or larger than negative nodes which was only 6.0 mm. Unfortunately, this difference of three mm. seemed to have no clinical value in differentiating between the positive and negative nodes because this three mm size difference was too small to be clinically recognized. Our study is consistent with the study of Ayhan et al[9] that there is a correlation between lymph node size and the frequency of tumor involvement. The percentage of tumor involvement increases from 1.0% when nodes are ≤ 3 mm to 21.5% when nodes > 20 mm. In term of positive nodes, the majority or more than half (59.6%) of these positive nodal long axis were less than 10 mm and most (90.2%) were less than 20 mm. This finding also agrees with other studies that the positive nodes need not to be large.[8,9,11,18,20]

As seen from Figure1., there was no appropriate cut off level for sensitivity and specificity. If we base on the widely accepted size 10 mm. of node as pathological enlargement, the specificity of 81% is more or less acceptable but the sensitivity of only 40% will lead us to miss 60% of the positive nodes if we use this 10 mm nodal size. Or if we set it at about 3 mm. which might be more or less valuable with the

high sensitivity of 94%, this has to be achieved only by removal of almost all nodes or complete lymphadenectomy. So we conclude from our study that lymph node size is a not reliable indicator in determining the presence of gynecologic cancer metastasis.

An interesting finding from the relationship of lymph node size and various histology finding is that the mean nodal long axis of positive nodes in adenocarcinoma group was much shorter than that of squamous cell carcinoma group (10.0 mm. versus 14.3 mm.). This confirms our hypothesis that lymph node size, especially in adenocarcinoma, does not correlate well with tumor metastasis. Since adenocarcinoma is the major histologic type of uterine and ovarian cancers so this further supports our opinion that selective approach of lymph node resection is inadequate for evaluation nodal status of these two cancers.

Another observation from our study was the median nodal long axis of positive nodes in germ cell and sarcoma groups were much larger than the negative ones 20.0 versus 6.0 mm. and 13.0 versus 7.0 mm. respectively. Nevertheless, the number of positive nodes yielded in these two groups were quite small (12 nodes from germ cell tumor and 11 nodes from sarcoma), so this result may need further study to explore its possible clinical implication.

In conclusion, though lymph nodes of larger size tend to associate with more risk of tumor metastasis than the smaller ones but this does not mean that the small nodes will be free from tumor metastasis. Our study has clearly shown that the majority of positive nodes can be small or smaller than expected and there is no good cut off point of nodal size with high sensitivity and specificity to determine tumor metastasis. These result in its poor clinical value. Other features as its consistency or nodal volume might help in differentiating them but they are also limited by the fact that the former is rather subjective and the latter may need more effort and require further prospective study. Until then, if one does not want to miss the accurate staging, its related prognosis and a proper plan of management, we strongly encourage complete lymph nodes dissection in all patients undergoing surgical staging. We also studied lymph nodes size separately for each type of gynecologic cancer and the results would be presented in the forthcoming papers.

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