What is the number of lymph nodes required for an "adequate" pelvic lymphadenectomy?

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Summary

Purpose of investigation: To establish a definition of an adequate number of lymph nodes identified at a pelvic lymphadenectomy through statistical methods.

Methods: We conducted a retrospective study in cervical and endometrial carcinoma patients who underwent radical or staging surgery. The Student's t-test, Pearson's correlation, analysis of variance, and linear regression analysis were used.

Results: Five hundred and ninety four-sided pelvic lymphadenectomies were analyzed. The mean (range) number of pelvic lymph nodes identifed was 11.3 (0-42). The 1st, 5th and 10th percentiles were three, five, and six lymph nodes respectively. The number of lymph nodes was higher in the laparoscopic approach compared to laparotomy (11.9 vs 10.6, $p < 0.01$).

Conclusions: The number of lymph nodes identified at a pelvic lymphadencetomy vary with type of surgery. We propose that using the 1st, 5th or 10th percentile is reasonable for the definition of an adequate number of lymph nodes to be identified at a pelvic lymphadenectomy.

Key words: Pelvic lymphadenectomy; Cervical carcinoma; Number of lymph nodes; Laparoscopy.

Introduction

Early stage cervical cancer is primarily treated by radical hysterectomy and systematic pelvic lymphadenectomy. The presence of metastases to lymph nodes is one of the most important determinants for the need for adjuvant therapy, and a strong predictor of survival [1, 2]. It is therefore extremely important that a complete pelvic lymph node dissection (PLND) be performed to minimize the number of false negative lymphadenectomies. This same philosophy applies to staging lymphadenectomies for other gynecologic malignancies such as endometrial and ovarian carcinoma.

However, the minimum number of pelvic lymph nodes (PLN) identified at a PLND to be defined as adequate has to our knowledge never been enunciated. Most studies only describe the total mean or median number of lymph nodes obtained from both pelvic sides [3-8].

The determinants of the number of lymph nodes have also never been formally explored. We questioned whether the number of nodes retrieved varied with body size, tumour site, type of surgery (laparoscopy vs laparotomy) or surgeon. We therefore set out to answer the above two questions through a review of prospectively collected data.

Material and methods

Since July 1, 1984 all radical surgeries performed for cervical carcinoma at the University of Toronto have been prospectively recorded and entered into a database. Patients with FIGO Stage Ia1 (with evidence of vascular space involvement), Ia2 and Ib1 cervical cancers were treated by radical surgery including PLND [9]. A description of the surgical procedure performed in our center for a pelvic lymphadenectomy has been previously published [10, 11]. As the database does not record the number of lymph nodes obtained, all patients from the database at one hospital had their respective pathology reports retrieved, and the number of lymph nodes identified on the pathology report recorded. Two surgeons are based at this hospital, and have been performing surgeries since 1988. Cases were excluded if the number of lymph nodes identified was not reported. To assess the impact of laparoscopy on pelvic lymph node yield, patients managed by a laparoscopic PLND and vaginal hysterectomy for endometrial carcinoma were also included in the study between the years 1995- 2001.

Grossing of resected specimens was performed according to the locally implemented protocols. The resected specimen was fixed overnight in neutral 10% formalin, following which an experienced pathologist assistant dissected it, while inspecting and palpating for any detectable lymph nodes. Identified nodes were bisected and submitted separately in designated tissue processing cassettes. The remainder of the resected adipose tissue was submitted in its entirety in a separate group of cassettes. A single hematoxylin and eosin-stained section was prepared from each processed paraffin-embedded tissue block.

The number of lymph nodes in each case was abstracted from the "diagnosis" section of the respective pathology reports. Numbers listed in the "gross description" section were disregarded since they were often revised following the pathologist's inspection of the stained histopathology sections.

Statistical analysis was performed using SPSS (Micro Master Software, Richboro, PA). As the data were normally distributed, parametric tests were used. The Student's t-test, and Pearson's correlation, were used. Statistical significance was defined as $p < 0.05$. As the number of lymph nodes identified was not clinically different between the right and left (mean 11.7 vs 10.9, respectively), the two sides were analyzed independently, doubling the number of sided pelvic lymphadenectomies from 297 to 594.

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Results

Two hundred sixty-four and 33 cervical and endometrial carcinoma patients, respectively, treated between 1988-2002 were analysed. Table 1 provides the details of the number of lymph nodes obtained. The mean number of PLN obtained from the cervical and endometrial carcinoma patients was 11.4 and 11.0, respectively (not statistically significant). A total of 30 (6%) cervical and six (9%) endometrial cancer patients had tumour metastatic to the pelvic lymph nodes.

Table 1. — *Yield of lymph nodes.*

N	594
Mean	11.3
Range	0-42
Percentiles - 1	3
5	5
10	6

There was no significant correlation between body mass index (BMI) and the number of pelvic lymph nodes identified by either analyzing BMI as a categorical variable (greater than or less than 30), or as a continuous variable.

Table 2 demonstrates the number of lymph nodes identified by the surgeons. The student's t-test did not demonstrate any significant difference in the number of lymph nodes retrieved between surgeon A or B.

Table 2. — *Differences in lymph node retrieval by surgeon.*

Surgeon	N	Mean	Range
A	496	11.41	0-42
B	98	10.74	1-30

Differences not significant.

One of the surgeons (A) has routinely performed laparoscopic PLND since 1995. To evaluate the differences in the number of lymph nodes retrieved by laparoscopy vs laparotomy, only surgeon A's data for laparotomy were analyzed (Table 3). Despite a smaller BMI in the laparoscopy patients (24.8 vs 27.9, $p = 0.0002$), the number of lymph nodes identified was higher via laparoscopy (11.9 vs 10.6, $p < 0.01$).

Table 3. — *Laparoscopic PLND vs Laparotomy*[1].

PLND	N	Mean	Range	p value[2]
Laparotomy	190	10.6	0-32	
Laparoscopy	302	11.9	0-42	0.001

[1]For same surgeon only; [2]Student's t-test.

Discussion

The most truthful method of determining a criterion for the minimum number of pelvic lymph nodes identified at pelvic lymphadenectomy to be defined as adequate would involve analyzing recurrence and survival in patients surgically treated. Unfortunately, in addition to the factors identified in this paper (surgeon, BMI, hospital, type of surgery) one would also have to control for adverse tumour factors and adjuvant therapies. Clearly such an approach would require thousands of patients and prove to be very difficult if not impossible. Therefore, surrogate methods such as statistical models have to be used.

Most studies published to date addressing the number of nodes identified at PLND in gynecologic cancers has focused on the incidence and distribution of lymph node metastases, and the mean/median number of nodes removed per patient. Studies with larger numbers of patients have been published by many authors including Benedetti (225 patients - median retrieval of 48 pelvic lymph nodes (range 20-107), and Sakuragi (208 patients - mean of 56.4 pelvic nodes (range 24-117) [3, 8]. However, most of the published studies quote the total number of lymph nodes retrieved combining both the left and right sides.

Most studies comparing laparoscopic surgery with laparotomy describe no significant difference in lymph node yield. However, in obese patients with endometrial carcinoma, Eltabbakh found a higher yield of PLND in laparoscopically staged patients versus laparotomy (11.3 versus 5.3, $p < 0.001$) [12]. The number of patients in that study however was limited ($N = 80$) and the PLND procedure was not described. Posseover also documented an increased yield of pelvic lymph nodes with a laparoscopic procedure vs a laparotomy [13].

A Gynecologic Oncology Group (GOG) has handled the adequacy issue differently in their prospective assessment of laparoscopic pelvic lymphadenectomy. In the study published below, laparotomies were performed subsequent to the laparoscopy, and a search for additional lymph nodes was performed. Subsequent GOG studies have required video or picture evidence of the completeness of the node dissection. Unfortunately, neither of the above approaches are feasible in clinical practice. The GOG published a study of 40 patients on laparoscopic PLND followed by laparotomy to determine the adequacy of the lymph node removal [14]. The mean number of right-sided nodes was 16.6 (range 4-41) and left-sided 15.5 (range 4-32). Six patients were judged as an incomplete PLND at laparotomy. None of the patients had lymph node metastasis in laparoscopically unremoved nodes. Nonetheless their conclusion was that the laparoscopic PLND demonstrated problems regarding adequacy. It is our experience that no matter how a pelvic lymphadenectomy is performed, one can always identify a small quantity of unremoved lymph nodes with further surgical effort. Naturally, this might reflect the learning curve for laparoscopic surgery [15, 16]. We have concluded from our data that a laparoscopic approach yields more lymph nodes than an open procedure.

One could argue that the hospital pathology department's grossing and reporting is a significant determinant of the number of nodes identified at surgery. It has been shown in breast cancer studies that immunohistochemical ultrastaging of lymph nodes identifies up to 15% of previously defined negative lymph nodes as metastatic. Although the implications of such micro-metastases may not be the same as typically identified metastases on

H&E staining, this fact is worthy of consideration in the concept of a false negative pelvic lymphadenectomy.

As far as these authors know there have been no attempts to establish a definition of the minimum number of lymph nodes to be obtained in order to consider the pelvic node dissection representative or adequate. In our study the median yield from a PLND by different surgeons in our hospital with typical pathology processing was 11.3 lymph nodes per side. The decision as to the number of lymph node required to be considered an adequate staging lymphadenectomy is arbitrary. Clearly there is little disagreement among gynecologic oncologists that the lack of identification of any lymph nodes in the surgical specimen from one pelvic side is an inadequate lymphadenectomy. Increasing the number of nodes identified above that will meet with some disagreement. In our opinion, we feel using the 5th or 10th percentile is reasonable. Whether an inadequate PLND necessarily leads to adjuvant therapy or a change in management needs to be addressed in the future. Ideally, we would have liked to correlate the number of lymph nodes with recurrence and survival. In breast and colon carcinoma a correlation between the lymph node yield and clinical outcome has been demonstrated [17-21]. We did not attempt this same analysis, due to the low number of positive lymph nodes, and the biases listed above, including the common use of adjuvant therapy for other high-risk features. The consequences of having a pelvic lymph node dissection that has been defined as inadequate include: repeating the procedure, administering adjuvant therapy, or nothing (ignoring the fact). Hopefully, other authors will examine and report similar statistics, thus enabling gynecologic oncologists to establish requirements for the minimum number of lymph nodes required for an "adequate" pelvic lymphadenectomy.

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