Assessing variations in lymph node recovery in colonic adenocarcinoma specimens: Results from a teaching and community hospital

By

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Assessing Variations in Lymph Node Recovery in Colonic Adenocarcinoma Specimens: Results from a Teaching and Community Hospital

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A Thesis/Practicum submitted to the Faculty of Graduate Studies of The University of Manitoba in partial fulfillment of the requirements of the degree

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II. LIST OF ABBREVIATIONS

CH	Community hospital
TH	Teaching hospital
CRC	Colorectal cancer
HNPCC	Hereditary non-polyposis colon cancer
TNM	Tumor node metastasis classification system
T	Tumor
N	Node
M	Metastasis
CAP	College of American Pathologists
LNRS	Lymph node revealing solution
WRHA	Winnipeg regional health authority
MW	Mann-Whitney statistical test
UTT	Unpaired t-test
NS	Not significant

III. ABSTRACT

This study examines the source of variation in lymph node recovery in patients with colonic adenocarcinoma. Low lymph node counts can affect the staging and clinical management of a patient with colonic adenocarcinoma. In some cases, it may lead to understaging of the disease and a subsequent decrease in survival. Review of the literature reveals that both gross pathological technique and surgical technique are contributing factors, as well as intrinsic patient variation. However, the majority of studies focus on pathological technique as the predominant factor in understaging. Although many studies have examined pathological technique in depth, no formal studies have investigated the role that surgical technique may play in low lymph node recovery. This may relate to difficulties in assessing surgical technique in an objective and standardized fashion.

Two hospitals in the Winnipeg Regional Health Authority (WRHA), one community hospital (CH) and one teaching hospital (TH) were chosen for this study. CH was chosen because previous analysis had established above average lymph node recoveries for that site. These were significantly higher than the lymph node recoveries at TH, and the aim of this study was to assess the relative contribution of pathologic and surgical factors in this difference.

Various parameters were utilized to assess the diligence of gross pathologic technique. Total lymph node numbers were documented and averaged. Additionally, percentages of lymph nodes measuring less than 5 mm and less than 3 mm were calculated. High percentages of small lymph nodes were felt to reflect diligent pathologic technique. These percentages were also compared to literature data. Lymph node

recovery data was divided into left and right side resections due to the anecdotal impression that lymph node counts would differ between these sides, and the belief that surgical factors might differ as well. Where right and left sided data was similar, it was pooled for statistical analysis.

Surgical technique was assessed through the measurement of mesenteric weight. It was assumed that differences in mesenteric weight would reflect differences in surgical technique in terms of segment length, "depth" of mesenteric resection, or both. Weights were grouped into right and left sided data sets. When no significant difference existed, both sides were pooled for statistical analysis.

Our results indicate a significant difference in average total node count between CH and TH (Left: 21.5 vs 13.3, p=0.0059, Right: 21.3 vs 12.4. p=0.0304). Despite this difference, similar nodal size profiles were achieved between CH and TH. A significant difference in mesenteric weights was found between CH and TH (Left: 325.2g vs 169g, p=0.0249, Right: 317.0g vs 135.3g, p=0.0039) with mesenteries at CH weighing twice that at TH. Furthermore, lymph node recoveries per 100g of mesentery were identical between the sites. This data leads us to conclude that variation in lymph node recovery between CH and TH in this study is predominantly, if not entirely, due to differences in mesenteric volumes (reflecting differences in surgical technique) between the sites.

This is the first study to examine the role of surgical technique in lymph node variations in a systematic fashion. We have established that greater mesenteric weights correlate with superior lymph node recovery. It is not clear that lower mesenteric weights result in understaging of a patient population, as node positive rates were statistically identical in the CH and TH populations (approximately 40% in both).

In the concluding chapter of this thesis, limitations of this study were noted. Due to the limited availability of stored surgical specimens the sample size varies between the two sites and the power of the study can be improved by increasing the number of specimens. Additionally, metastatic status was not controlled for in this study. It is theoretically possible that a population with higher rates of known metastatic disease would undergo more "palliative" resections, with a less rigorous surgical technique. Finally, patient weights were not controlled for, and patient weight may affect mesenteric weight.

This study suggests that mesenteric weight should be incorporated into minimum lymph node recovery standards and should be a routine component of pathologic evaluation in all colorectal resection specimens.

IV. INTRODUCTION

Colorectal carcinoma (CRC) is a major cause of morbidity and mortality in North America and Europe (1). It is the second commonest visceral malignancy, with the second greatest mortality, behind lung carcinoma. Almost all colonic carcinomas are adenocarcinomas (1). Rates are much lower in Asia and Africa, and dietary/lifestyle differences are felt to be significant in the development of colorectal malignancy. High-fat low-fiber diets are significant; additionally, numerous genetic syndromes are associated with colorectal adenocarcinoma. These include polyposis syndromes and hereditary non-polyposis colon cancer syndrome (HNPCC). Additionally, inflammatory bowel disease is a significant risk factor for CRC. A family history of colorectal cancer in a first degree relative is significant, particularly in younger individuals (50 years or less in age) (17). Nonetheless most patients with CRC have neither a family history, polyposis, or a cancer syndrome. The great majority of CRCs are sporadic (17).

The incidence of colonic adenocarcinoma rises significantly with age, with the highest incidence in the 70-85 year old age group. Only 5% of CRCs occur in patients under 40. Nonetheless it is one of the most common adult-type visceral malignancies in this age group (1). The incidence is high enough after 50 years of age to justify routine surveillance strategies in the general population (16). Controversy exists as to the most cost effective surveillance strategy. Proponents support routine colonoscopy, flexible sigmoidoscopy and fecal occult blood testing, alone or in combination. However despite the fact that colon cancer is a highly preventable disease with a well established precursor lesion, routine screening is not routinely practiced in North America or Europe.

It is generally accepted that CRC arises from a benign precursor lesion called an "adenoma". Adenomas are intramucosal epithelial tumors which have not invaded into underlying tissues and are not biologically malignant. They are usually polypoid growths which can be detected by routine surveillance. The most sensitive surveillance technique is colonoscopy. In this procedure an endoscope is passed per anus and the entire colon is visualized. Any identified adenomas are biopsied and removed. Removal of polyps has been shown (class I evidence) to reduce the incidence of invasive carcinoma in a screened population (16). Adenomas are found in up to half the population over 40 years of age. A significant minority, if not removed, will evolve into invasive CRC.

As cancers grow, they invade sequentially through the layers of the muscle wall, finally extending full thickness through wall into pericolic or perirectal fatty tissues. They can also involve colonic serosa and adjacent structures by direct extension. As the tumor grows the likelihood of lymphovascular invasion increases with metastasis to regional lymph nodes and distant organs (1). Once the tumor has spread outside the bowel wall, metastatic potential and mortality increases significantly. Common sites of metastasis for CRC include the brain, lung, liver, bone, skin and ovaries. If regional lymph nodes are positive the prognosis further deteriorates. Patients with tumors extending through wall without lymph node involvement have approximately 80% long term survivals. Lymph node involvement decreases survival to approximately 50%, with increased number of involved nodes resulting in a progressive deterioration in survival statistics (4).

Treatment options include surgery, chemotherapy, and radiotherapy. Surgery remains the definitive therapy for potentially curable disease, defined as disease which can be surgically resected and demonstrates no evidence of metastatic disease after full

clinico-pathological staging (8). Surgical resection of CRC involves en bloc removal of the tumor containing colon segment with adequate proximal, distal and radial (for rectum) resection margins. The related mesentery is also resected with its associated lymph nodes. Generous mesenteric excisions are the standard in order to assure accurate staging of the patient.

In order to determine the proper treatment, and establish an accurate prognosis, adenocarcinoma of the colon must be accurately graded and staged. Histological grading of a tumor involves assessing various features of the tumor such as degree of differentiation, growth pattern, mitotic rate and degree of pleomorphism, features which have been shown to affect prognosis. Tumor staging combines pathological and clinical findings to define a formal tumor stage (I, II, III, or IV). Tumor stage affects both prognosis and use of ancillary therapies such as chemotherapy or radiotherapy.

Adenocarcinoma of the colon is divided into four Stage Groupings. The four stages are based on the assessment of 3 types of pathologic and/or clinical parameters: tumor size (T), nodal status (N), and distant metastatic status (M). Together these parameters make up the TNM system, a method of cancer staging which has been recently standardized and adopted by both American (American Joint Committee on Cancer) and European (International Union against Cancer) cancer organizations. Tumor and nodal status is determined (at least in potentially curative cases undergoing resection) by pathologic examination. Metastatic status can be determined by pathologic examination or by imaging techniques. Adherence to this standardized staging protocol has been mandated by the American College of Surgeons, and all American hospitals performing cancer related surgeries must use this system in order to be accredited.

Furthermore, the College of American Pathologists (CAP) has formally adopted the TNM system as the only acceptable system for pathologic cancer staging (16).

In brief, Stage I CRCs are restricted to the bowel wall with no lymph node involvement. These carcinomas have an excellent prognosis with over approximately 95% survival. Stage II carcinomas extend through bowel wall (to varying degrees) without nodal involvement. Survival remains good in the absence of serosal involvement, but depends on the extent of extramural invasion. Stage III carcinomas all have lymph node involvement and a much poorer prognosis. Stage IV carcinomas are cases with metastatic disease. Outside of certain unusual clinical situations (such as a solitary metastasis to liver or lung which can be surgically resected) metastatic disease is invariably fatal, although the clinical course can be prolonged. Tumors are substaged within these groups depending on exact T and N status. [see Tables VIII.1 and VIII.2]

Consequently, diagnosis and treatment of CRC depend predominantly on variables reported in the surgical pathology report. Accurate information requires meticulous gross specimen evaluation by the Pathologist/Pathology Resident/Pathologist Assistant. Staging variables influence treatment decisions and prognosis. Most importantly from the therapeutic point of view is that node positive patients receive ancillary chemotherapy (16). This therapy has been shown to improve survival in node positive patients. Therefore, patients with higher-stage disease who are incorrectly diagnosed with a lower-stage adenocarcinoma may not receive appropriate or sufficiently aggressive treatment for the prevention of local recurrence or metastases. More recently, serosal positivity (T4 disease) has also been shown to significantly decrease survival, even in the absence of positive nodes. Therefore, patients with stage IIB disease are often

receiving chemotherapy as well. Any survival benefit has not yet been definitely established.

Lymph node recovery in colorectal specimens is done by a Pathologist, Pathology Resident, or Pathologist Assistant. Studies have shown that the quality of a gross examination differs between these individuals. This will be discussed further in the literature review. Lymph node recovery in colorectal specimens is accomplished through manual examination of mesenteric fat which has been carefully dissected off the adjacent colon. The fat is sliced at 3-4 mm intervals, laid flat on a cutting board and carefully palpated. In many cases small nodes are picked up by palpation as opposed to visual inspection. Careful dissection can pick up lymph nodes as small as 1mm in transverse diameter. The great majority of mesenteric lymph nodes are less than 1cm in size with over 50% measuring 5 mm or less in a high quality dissection (13). The number of lymph nodes reported in colectomy specimens varies widely, and many lymph node counts fall below minimum numbers mandated by the CAP for an adequate lymph node examination (12 nodes minimum). This deficiency is significant not only in terms of failing to meet standards of practice but in terms of affecting patient prognosis and treatment. Patients with low node counts (even if node negative) are known to have a poorer prognosis than node negative patients with higher counts (4). Additionally some clinicians will treat node negative patients with chemotherapy because of concerns over under-staging. The reasons for low node counts are multiple, and the relative contributions of the various factors are unknown. Possible factors include poor grossing technique, differences in surgical technique resulting in variations in amount of mesenteric fat, and intrinsic variation in lymph node numbers between patients.

IV.1 Literature Review

The significance of maximizing lymph node yields in patients with colorectal adenocarcinoma has been examined in numerous studies. The consensus is that variations in lymph node yields exist which affect the prognosis of CRC patients. In a study done by LeVoyer et al (8) a secondary analysis was conducted on a mature trial of adjuvant chemotherapy for high-risk patients with stage II and stage III colon cancer to determine the relationship between survival and the number of lymph nodes analyzed from surgical specimens. The main predictor of outcome used was overall survival. In all, 3561 patients were eligible. Statistical analysis of data was conducted, and revealed that survival of patients increased as more lymph nodes were analyzed ($p=0.0001$), and that survival decreased with increasing number of lymph node involvement ($p=0.001$). Even with uninvolved nodes over-all survival increased ($p=0.0005$). This suggests that the number of lymph nodes analyzed is a significant variable that affects survival in both node-negative and node-positive patients, and that survival rate improves as more nodes are removed, regardless of the number of positive nodes. They concluded that the number of lymph nodes analyzed for staging colon cancers is itself a prognostic variable. It was hypothesized that lymph node recovery could be due to two factors, one being the surgeon and the other being pathological examination. The first factor was based on the idea that experience and specialty expertise varies from surgeon to surgeon, with higher lymph node counts being attributed to high volume specialists. However, data to support this conclusion was not generated. Rather, pathological technique was considered as the more likely contributor to lymph node count variations. Care taken by the Pathologist in finding lymph nodes and the examination method used by the Pathologist were both put

into question. Le Voyer suggested in his discussion that techniques other than the manual dissection method would yield much higher lymph node numbers. He quoted Hermanek et al as stating that lymph node recovery can be improved by fat clearance techniques. The fat-clearance technique used by Hermanek et al on average presented 47 lymph nodes. In this method, the mesenteric fat is put into a clearing solution. The fat present is dissolved and lymph nodes remain intact. Even without the fat-clearance technique the average node count was 31, still significantly higher than Le Voyer's study which identified an average of 13 lymph nodes in both node-positive and node-negative groups. Given such data, it implies that some difference in pathological technique accounts for differences in lymph node yields. Hence the focus in this study was on pathological technique rather than surgeon variability.

Le Voyer et al's findings were similar to those of Brown et al (2). Their study also noted variations in lymph node yields and lymph node metastases despite claims of meticulous searches. Like Le Voyer et al, pathological technique was hypothesized as the source for the variation. The efficacy of the gross dissection was tested by submitting the entire residual mesenteric fat for microscopic study. A random selection of 15 colonic adenocarcinoma resections was analyzed by standard gross dissection followed by dehydration of the remaining mesenteric material. The entire mesentery was then submitted for histological examination. Microscopic sections were examined independently by two Pathologists to identify the number and size of lymph nodes as well as the presence of any metastases. The average number of additional nodes found after complete submission was 68.8, with a range of 37-112 compared to an average of 20.8 nodes found using the standard manual technique. Almost 83% of these additional lymph

nodes measured less than 2mm and 50% measured less than 1mm. Submission of the mesenteric material in cases with lymph node involvement (N1) resulted in 3 out of 4 cases being upstaged to N2. These findings showed that a manual dissection proved sufficient for N0 tumors as none of the N0 cases were upstaged, but in the case of N1 tumors, examination of all the mesenteric material may be necessary to be assured of accurate N staging. The results from this study can prove to be valuable when assessing pathological technique and the lymph node variations with each sampling method. A good predictor of pathological technique was identified as diligence in finding lymph nodes measuring less than 2mm in greatest dimension.

Although manual dissection was sufficient in grading N0 tumors in the Brown study, clearing techniques have been shown in other studies to be valuable in upstaging patients. In the study by Hida et al (5) the lymph node count and lymph node metastases was compared between the clearing technique and the manual method. Compared with the manual technique, the clearing technique provided 4 times the number of nodes and an increased node positive rate of 19.3%. These differences were attributed to the detection of metastatic nodes smaller than 4 mm by the clearing technique. Although the clearing method seemed useful, the study did not look further at the effect on prognosis.

The efficiency of clearing techniques was also examined in the study by Ustun et al (15). Ustun et al used a lymph node revealing solution (LNRS) in which specimens were immersed in LNRS until the fat dissolved and the remaining lymph nodes were dissected out. The results of this study demonstrated that LNRS increased the number of total and metastatic lymph nodes significantly ($p<0.01$). However, significant upstaging from N0 to N1 did not occur. Rather, upstaging of N1 to N2 was identified. This increase

in node positive identification was therefore of limited clinical or therapeutic importance. As in other studies, LNRS treatment detected higher numbers of small lymph nodes compared to the manual method. This study concluded that the clearing method is useful for accurate staging where the number of detected lymph nodes is unsatisfactory by the conventional method. Similar conclusions were drawn by Brown et al in which total submission of mesenteric fat was suggested as an appropriate second measure to take in cases with low lymph node recovery.

The importance of small (<2mm) lymph node recovery was supported in a study done by Goldstein (4). In this study, he examined the role of lymph node numbers in node negative patients, and the relationship between increasing lymph node numbers and N status. A retrospective study was conducted with an ample sample size of 2427 surgical specimens. In this study, the number of recovered lymph nodes was significantly associated with both presence and percentage of lymph node metastases. The association between an increasing number of recovered lymph nodes and increasing percentage of specimens with lymph node metastases remained statistically significant among specimens with 12 or more recovered lymph nodes. This and other studies confirm that recovering greater numbers of lymph nodes from colon specimens has clinical importance and an effect on patient management. They also suggest that a minimum standard number of recovered lymph nodes that is adequate to accurately identify all patients with regional lymph node metastases does not exist. No clear-cut number of recovered lymph nodes would identify most patients with lymph nodes metastases. Instead, all lymph nodes from colon resection specimens should be recovered to accurately evaluate whether lymph node metastases are present. An advantage of the

Goldstein study is that tumors were restricted to T3 stage. Other biases were also avoided by excluding total colectomy and extended resection specimens.

It has also been hypothesized that variations in lymph node counts can be attributed to the volume of specimens at different sized hospitals (10). Miller et al conducted a study also supporting LeVoyer et al's conclusions of a positive association between increased survival rates with the number of lymph nodes recovered. In patients positive and negative for lymph node metastases survival rates were found to be lower in patients with less than 7 lymph nodes recovered compared to patients with more than 7 lymph nodes recovered. Comparisons according to hospital volume showed that low-volume hospitals were twice as likely to recover less than 7 lymph nodes compared with medium and high volume centers. Low-volume hospitals were also three times less likely to detect positive lymph nodes. No firm conclusions were drawn as to the relative role of surgical or pathologic technique, although an implication of poor quality microscopic examination in low volume hospitals was made. A study conducted by Johnson, Malatjalian, and Porter found that surgical volume was an important factor in lymph node recovery, while pathologist volume was not significant. This study is flawed by a low average node recovery. Overall, the data verifies that variations in lymph node recovery according to hospital volume do exist. It suggests that patients at low-volume hospitals are at a higher risk of having their disease under-staged compared with patients at higher-volume hospitals (7). Despite the Johnson, Malatjalian, and Porter paper, the importance of surgical volume in colon cancer lymph node recovery is relatively weak. Overall, the literature strongly implies that pathologic factors are paramount.

Interestingly, the Johnson, Malatjalian, and Porter study also cites an association between examination of specimens by a staff Pathologist and higher node recovery compared to a Pathology Resident/Pathologist Assistant. This disagrees with the experience of Galvis et al (3) that Pathologists' Assistants perform exemplary gross dissections. These differing interpretations would appear to relate to the low overall recoveries in the Johnson Study. (8.3 vs 31.3). The goal of the Galvis et al study was to measure the quality of services provided by a Pathologist Assistant. Their performance was compared to Pathology Residents by using the criteria of lymph node retrieval and tissue resubmission rates. Total numbers of lymph nodes retrieved, number of positive nodes, and length of colorectal specimens were all obtained from final surgical pathology reports. The results of this study revealed that on average Pathologists' assistants recovered significantly higher total node counts than Pathology Residents, although there was no significant difference in the total numbers of positive lymph nodes retrieved (3). This suggests that gross examination by Pathology Residents and Assistants did not result in differences in pathologic staging relating to lymph node status. From a clinical standpoint, both Pathologists' Assistants and Residents performed equivalent gross examinations. The tissue resubmission rates revealed that statistically significant fewer cases were resubmitted after the initial examination when a Pathologist Assistant performed the examination compared to a Resident. When this marker was used, Pathologists' Assistants demonstrated superior performance compared to Residents. A potential limitation of this study is that it was performed at a single center with participation by only two Pathologists' Assistants. In addition, comparisons with Pathologists were not included even though staff Pathologists assisted with select cases.

These findings demonstrated that the quality of Pathologist Assistant services is equivalent to or superior to that of Pathology Residents. These results are important to this thesis because a major difference between the two sites compared in this study is the availability of residents ie. teaching hospital vs. community hospital. Due to small sample sizes, specimens grossed by Pathologists' Assistants and Residents were not separated in the TH sample.

As previously noted low lymph node counts can be due to poor pathologic grossing technique, differences in mesenteric volume, surgical technique, and intrinsic variations between patients. As literature studies have shown marked differences in lymph node recovery rates between different hospitals with similar populations it can be assumed that the last factor has been controlled for. Therefore, the two main reasons for differences in lymph node recovery between sites are pathologic or surgical technique. The general assumption in the literature is that differences relate predominantly to pathologic technique. However, no studies in the literature to our knowledge have specifically addressed the issue of variations in surgical technique in a systematic fashion.

IV.2 Hypothesis & Objectives

It is hypothesized that variations in both pathologic and surgical technique contribute to previously established differences in lymph node counts between institutions in the WRHA. The aims of our study are as follows:

-To analyze lymph node recovery numbers in two WRHA hospitals, one teaching and one community, both of which have relatively high volumes of colorectal surgery.

-To utilize various parameters to assess the completeness of the lymph node dissection, the primary discriminator being number of nodes under 5mm, and under 3mm detected.

-To assess surgical technique through the parameter of mesenteric weight. We hypothesize that greater mesenteric weights will correlate with superior surgical technique and increased lymph node recovery. Controlling for mesenteric weight will allow us to directly compare pathologic technique between sites.

V. MATERIALS AND METHODS

V.1 Surgical Specimens

Hospital databases were used to retrieve Pathology reports for colonic adenocarcinoma specimens. Pathology reports were gathered from one teaching hospital (TH) and one community hospital (CH). Sample sizes obtained from each site were dependant upon hospital policies regarding minimum length of storage time for processed surgical specimens. CH stored surgical specimens for up to two years after processing resulting in 130 specimens available for use in the study. Specimens collected from CH date from October 25, 2002 to April 6, 2004. TH stores surgical specimens for one year resulting in 35 available specimens. Specimens collected from TH date from November 31, 2003 to November 16, 2004. Cases included in this study were restricted to invasive adenocarcinoma diagnosed in resection specimens with attached mesentery. After exclusion of irrelevant specimens such as polyps or biopsies, the samples sizes for CH and TH were 72, and 31 respectively. Specimens were not matched as to patient demographics. Colonic specimens from both sites were separated into left and right colon. Right colon was defined as cecum, ascending colon, +/- transverse colon. Left colon was defined as sigmoid and descending colon. All rectal resections and specimens including rectum were omitted. In cases of total colon resections or resections that did not fit the description of the designated categories, specimens were assigned based on the location of the tumor.

V.2 Mesenteric Weight and Length

Total mesenteric fat from each surgical specimen was weighed using a standard electronic scale. Specimens stored in formalin fixative were strained and partially dried.

Remaining contents were examined. Omentum and fragmented colonic/ileal tissue were excluded from the weight measurements. Mesenteric fat still adherent to any large bowel segments was cleanly stripped and removed and included in the measurement. Mesenteric weight was also correlated with specimen length, the data for which was provided in the gross description of the pathology reports.

V.3 Lymph Node Count and Status

Total lymph node counts and nodes positive for metastases were taken from the final pathology report findings. For each case, microscopy slides were obtained and examined. The greatest dimension of each lymph node was measured and recorded with a standard scientific ruler. The nodes positive for metastasis were identified and their sizes were separately recorded. Lymph node sizes were categorized as follows: >1 cm, 0.5-1.0 cm, < 5mm, <3mm

V.4 Statistical Analysis

Significant differences between CH and TH for mesenteric weights, total lymph node counts, and percent positive nodes were determined using unpaired two tailed t-tests. Comparisons between CH and TH for nodal parameters [lymph nodes measuring less than 5mm and less than 3mm, nodes per 100g mesenteric weight] were carried out using the MannWhitney U-test due to small sample sizes and an uneven distribution. All analysis was done using the biostatistical software Graph Pad Prism, version 3.03.

VI. RESULTS

VI.1 Mesenteric Weight and Length

Mesenteric weights from CH averaged 317.0g and 325.3g for left and right sided resections respectively. Compared, TH averaged 135.3g and 169.0g for left and right sided resections respectively. Differences between weights in TH and CH specimens were statistically significant (p=0.0249, left and p=0.0039 right). Weights at CH ranged from 32g-1064g on the left side and 63g-1078g on the right. At TH, weights ranged from 11g-350g on the left and 45g-726g on the right. [see Fig IX.5] The number of lymph nodes per 100g of mesenteric weight was calculated as follows: CH right (6.6), CH left (6.7), TH right (7.8), TH left (9.1). No significant differences were found between TH and CH. The associated length of resected specimens was also taken from the pathology report. No significant difference in average length was found with lengths at CH averaging 25.6cm and 26.8cm for left and right sided specimens respectively. Those of TH averaged 22.5cm and 18.2cm for left and right sided specimens respectively. [see Table VIII.3]

VI.2 Lymph Node Counts

The first parameter examined was the average total number of nodes found. For CH the total number of nodes averaged 21.3 and 21.5 and TH averaged 12.4 and 13.3, for left and right side respectively. These differences between TH and CH were statistically significant (p=0.0059, left and p=0.0304, right). [see Fig IX.1] The number of cases with less than 12 nodes recovered was calculated as a percent of total cases. [see Fig IX.2] At

CH, 29.4% and 18.4% of cases had less than 12 nodes recovered for left and right side respectively. At TH, 64.6% and 35.7% of cases had less than 12 nodes recovered for left and right side respectively. [see Table VIII.3]

VI.3 Lymph Node Size: <5mm, <3mm

The percentages of total nodes measuring less than 5mm at CH were 69.4% on the left side and 63.5% on the right side. The difference between left and right side was statistically significant with p=0.0114. At TH the percentages were 87.1% for the left side and 58.6% for the right side, and were also statistically significant with p=0.0012. [see Fig IX.3]Combining the data from left and right side, there was no overall significant difference between CH and TH in the percentage of total nodes measuring less than 5mm. A more rigorous parameter was established with nodes measuring less than 3 mm in greatest dimension. The percentages of total nodes at CH measuring less than 3 mm were 33.2% for the left side and 26.1% for the right side. The difference between left and right side was statistically significant with p=0.0372. At TH the percentages were 46.7% on the left side and 23.7% on the right, with a statistical significance of p=0.029.[see Fig IX.4] Combining the data from left and right side, there also was no overall significant difference between CH and TH in the percentage of total nodes measuring less than 3mm. [see Table VIII.3]

VI.4 Lymph Nodes Positive for Metastasis

The percentage of total nodes which were positive for metastases was highest among right sided colon resections at the TH with 15.1% compared to 9.2% at the CH.

CH had 8.2% of the total nodes with metastases compared to 5.7% at TH for left sided resections. The combined average of nodes positive for metastasis at TH and CH was not statistically significant with p=0.9341. Of the total lymph nodes with metastases, the percentage of metastatic lymph nodes measuring less than 5mm was 49.2% and 66.7% for left sided specimens at CH and TH respectively. For right sided specimens they were 28.0% and 39.3% at CH and TH respectively. Metastases in nodes less than 3 mm had the following percentages: Left sided resections at CH and TH respectively were 16.9% and 25.0%, right sided resections at CH and TH respectively were 6.7% and 10.7%. Metastases were minimal in nodes measuring less than 2 mm. The percentage of cases with positive lymph nodes identified at CH averaged 44.4% compared to an average of 41.9% at TH. [see Table VIII.3]

V.5 Statistical Analysis

See table VIII.4

VII. DISCUSSION

VII.1 Summary

The survival of patients with colon cancer can be affected by multiple prognostic factors. The presence of lymph node involvement is undeniably the most important prognostic factor in patients undergoing a potentially curative resection (8). A single positive node affects prognosis negatively. Additional positive nodes result in a progressively poorer prognosis. Positive lymph nodes are an indication for ancillary chemotherapy, which has been prospectively shown to improve survival in node positive patients. Therefore accurate nodal staging is of paramount importance for the treatment of these patients. Additionally, recent studies have correlated increased numbers of lymph nodes recovered with improved overall survival in node negative patients with T3 disease (4). This is assumed to represent more accurate pathological staging in patients with increased node numbers, although this has never been definitively established. Because of this belief, some oncologists will treat node negative patients with low counts with ancillary chemotherapy (1). Chemotherapy has a significant morbidity and mortality, and is not the usual standard treatment for lower stage disease.

Much debated is the establishment of a minimum lymph node count from colon resections. The College of American Pathologists (CAP) mandates a minimum node recovery of 12 nodes, with mandatory documentation of re-examination in cases with lower counts. In cases with higher node recoveries rigorous examination in order to submit all identifiable lymph nodes is required. The CAP recommendation for re-examination implies that the main reason for low node counts is pathological technique.

However both diligence of pathological examination and differences in surgical technique contribute to differences in lymph node recovery. Surgical technique has been identified as a source, but in-depth analysis has not been carried out.

This thesis reports the results of a study of lymph node differences in patients with colonic adenocarcinoma at two WRHA sites (Winnipeg, Manitoba). The purpose of the research was to discover potential sources of variations in lymph node counts, such as pathological and surgical techniques. We proposed that mesenteric weight can be used as a marker to assess surgical technique, and pathological technique can be assessed using lymph node profiles. To our knowledge, our study is the first to examine surgical technique in a standardized fashion. Our data supports the interpretation that differences in mesenteric weight are primarily responsible for differences in node recovery between the two examined sites, and for the unacceptably low lymph node count at TH.

Pathological technique is continuously discussed in the literature as the primary source of variation in lymph node counts. Both individuals responsible for lymph node dissections and the techniques they use have been identified as the major contributors to differences in node counts (8). Currently, the majority of dissections are carried out by trained Pathologists' Assistants who tend to be more diligent in maximizing node counts and perform more complete examinations. Pathologists and Residents vary in their diligence, skill and patience when dissecting out lymph nodes from a surgical specimen. In many cases, time poses a constraint for the Pathologist. The high quality of gross examinations as achieved by Pathologists' Assistants is supported by Galvis et al (3). The minimum size of lymph nodes pursued in a dissection can also contribute to variations. Obtaining nodes as small as 1 to 2 mm can affect the overall node count, and in some

cases these limits are pursued meticulously, as in the study by Goldstein (4). The technique used to recover lymph nodes can also affect the quality of a dissection and can be a contributing factor to lymph node variations. Two pathological techniques for recovering lymph nodes have been described in the literature. The clearing method recovers lymph nodes with the aid of a lymph node revealing solution in which mesenteric fat is dissolved while the lymph nodes remain intact. The disadvantage of utilizing the clearing method as cited in the literature is the time, effort and expense required. Because clearing provides a high output of lymph nodes, past studies have suggested it as useful in re-examination of cases with inadequate lymph node recovery (5,6,11,15). The more conventional method used is manual dissection which involves careful visual inspection and palpation (2). Both CH and TH utilize this technique. The meticulousness in palpation by the Pathologist Assistant can vary with manual dissection. It is general practice to strip mesenteric fat as close to the bowel surface as possible. In our study, it was found that all specimens from CH were cleanly stripped of adherent fat, but at TH some dissections were done without removal of the mesenteric fat. Dissections in this manner could negatively affect lymph node yield because a complete inspection and palpation would be difficult.

VII.2 Pathologic Technique

In this study, examination of pathological technique from both sites demonstrated above average diligence in comparison with the literature. The results indicated that on average TH recovered 12.8 nodes while CH recovered an average of 21.4 nodes. Average node recovery at CH of over 21 nodes is substantially higher than the literature average.

[see Fig IX.1] In addition, less than 30% of the cases at CH had node counts less than 12, and node recovery was essentially equal between the left and right sides. Examination of the TH data reveals apparently poor lymph node recovery, with substantially higher (approximately 50%) suboptimal recovery. [see Fig IX.2] However, examination of the lymph node profiles showed that both CH and TH achieved high quality dissections. A high quality dissection has been defined as one with approximately 50% of the total nodes measuring 5 mm or less (13). Firstly, TH and CH achieved more than 50% of the nodes measuring less than 5 mm. Secondly, comparisons between TH and CH data (left, right and combined) in the percentages of nodes measuring less than 5 mm and 3 mm showed no significant difference. Furthermore, lymph node recovery per 100g of mesentery is higher at TH, although not statistically significantly more than CH. These impressive results are to be expected. 90% of all gross dissections at CH are performed by a single experienced (15 years) Pathologist Assistant. At TH, grossing duties are performed by four individuals all trained by one senior Pathologist Assistant (over 20 years experience).

Although there were no major differences between the hospitals, it is interesting to look at the differences between left and right sided resections within each hospital. Percentage recovery of small lymph nodes in left side resections (less than 5mm and 3mm) is extremely high in the TH population (87% and 47% respectively). This is actually higher (though not statistically significant) than small node recovery at CH (69.4% and 33.2% respectively). Comparing data at CH shows that the percentage of nodes less than both 5 mm and 3 mm are slightly higher in the left side by 5.9% and 7.1% respectively. These differences were statistically significant with $p=0.0114$ and $p=0.0372$.

Of interest is the fact that at TH, the percentage of nodes less than 5 mm and 3 mm was significantly higher in the left sided specimens (by 28.5% and 23% respectively with $p=0.0012$ and $p=0.029$). [see Fig IX.3 and IX.4] One explanation for this difference is that left sided examination was more rigorous due to the Pathologist Assistant's realization that low lymph node recovery is more common at this site. As a result, the differences can be attributed to a more rigorous examination producing increased numbers of smaller nodes. This interpretation is supported by the higher lymph node recovery per 100g on the left side vs. the right (9.1 vs 7.8). At CH node recoveries per 100g mesentery were almost identical between left and right side (6.7 vs 6.6). Specimen re-examination would also be more likely in TH left sided specimens, particularly in view of the CAP node recovery minimums. However, there is no formal policy documentation of re-examination at TH, making it impossible to estimate the significance of this factor. Presently, CAP guidelines mandate documentation of such re-examination in the pathology report.

Lymph node dissections are often time consuming and laborious and these constraints can negatively affect the quality of a proper dissection. Achievement of minimum lymph node counts should not affect the diligence of the remainder of the examination. A maximal effort should be maintained to recover all lymph nodes throughout the specimen.

VII.3 Surgical Technique

The role of surgical technique in lymph node recovery has been mentioned in passing in the literature but not assessed in a systematic fashion. A literature review has

documented no studies utilizing mesenteric weight as a marker of surgical technique. Low lymph nodes counts have been felt primarily to be secondary to pathological technique (8). In our study variation in lymph node recovery is almost entirely due to differences in the submitted surgical specimen. The standard surgical resection of colonic adenocarcinoma requires excision of the primary tumor, adjacent colon with safe distal and proximal margins, and associated mesentery containing lymphatic channels and nodes. Currently, there are no set guidelines as to standard amounts of mesentery submitted with colon resections. The surgeon must assess various properties of the tumor, such as size and aggressiveness to determine what mesenteric margins would be adequate. As a result this can lead to differences in the amount of mesentery attached to surgical specimens due to surgeon experience and expertise. Obviously wider mesenteric excisions will result in higher lymph node recoveries, given equal diligence of pathologic examination.

We believe that mesenteric weight is a reasonable indicator of differences in surgical technique. Weight is preferable to length as the latter does not allow individual variation in mesenteric depth. Controlling for mesenteric weight also allows us to compare pathologic technique as discussed above. Initially, the data sets at both sites were divided into left and right sides due to anecdotal impression that mesenteries would be more expansive on the right. As this proved to be an inaccurate assumption the data sets were pooled for statistical analysis. Average mesenteric weights were markedly higher at CH, both on the right (1.9 times) and the left (2.3 times). Right and left colonic mesenteric weights were relatively equal within sites. At CH the average right colonic mesentery weighed 325g and the left weighed 317g. At TH the average right colonic

mesentery weighed 169g and the left weighed135g. Average combined mesenteric weight at CH is 321.4g and TH is 150.5g. These differences are highly statistically significant ($p=0.0002$) despite the relatively small sample size. [see Fig IX.5] Average specimen length was also compared. Specimen lengths at CH were on average longer than at TH, but the difference was not as striking as the weight differences. These lengths averaged 26.2 cm and 20.5 cm at CH and TH respectively. These results establish that mesenteric weight is a crucial parameter in lymph node recovery. In both sites, pathological assessment was determined to be diligent by established techniques. Lymph node recovery was essentially equivalent per 100g mesentery between the sites. In fact, there was a trend towards increased recovery per mesenteric weight at the TH despite substantially lower overall counts. These differences in mesenteric weight suggest a significant role for surgical technique in the variation between TH and CH.

VII.4 Limitations & Implications

In assessing the reasons for decreased mesenteric weight at TH several possibilities must be considered. This study did not control for patient weight, and lower patient weights at TH could conceivable result in lower mesenteric weights. A second possibility is that the TH population included more patients discovered not to be curable at surgery. In such patients the colectomy would be palliative and a lesser effort would be undertaken to achieve a wide mesenteric excision. This suggests a limitation of this study, as final TNM status has not been controlled for. Assuming that neither of these factors is significant, the final remaining factor is differences in surgical technique between TH and CH surgeons. A minor component of the weight variation is colonic length (on average

22.3% shorter at TH) however the great majority of the difference must relate to the depth of the excision (ie extension along the mesenteric root). Reasons for these differences remain speculative. Review of the literature reveals no formal studies on differences in surgical technique (and between surgeons) relating to node recovery. However one can speculate that differences in surgical demographics may play a role. At CH, colorectal surgery is performed by four experienced surgeons with a minimum of 5 years experience, all of whom maintain a fairly high volume of colorectal surgeries. Residents occasionally rotate, but almost all colorectal surgery is performed by staff surgeons. At TH, most colorectal surgery is performed by residents, with staff supervision. Furthermore, in relation to the number of staff and residents, volumes of colorectal surgeries at TH are relatively low. It is conceivable that differences in experience and on-going exposure can explain the weight variations. This hypothesis is supported by the fact that weight variation is greatest on the left (2.3 times vs 1.9 times) since sigmoid resections are more technically demanding overall than right hemi-colectomies.

These findings do not eliminate the role of pathologic technique in lymph node recovery variations. Extensive literature has established that adequacy of pathologic technique varies between individuals. In general, Pathologists' assistants achieve greater lymph node numbers than residents or staff pathologists, in that order (3). Some of these differences relate to time constraints in the latter two groups. Nonetheless in this study, data shows that pathologic technique does not play a role.

A crucial point to be considered in this discussion is whether lower lymph node counts related to differences in surgical technique have an effect on staging. Specifically,

do lower mesenteric weights result in understaging of patients. In our study node positivity rates were essentially identical between the two populations (44.4 at CH vs 41.9 at TH). The sample size of this study however, makes it difficult to draw a definite conclusion. Larger numbers would be required before definitely stating that lower mesenteric weights do not result in pathologic understaging. Of interest is the apparent difference in nodal positivity at CH and TH on the left side (41.2 vs. 29.4). However this difference is not statistically significant. This data suggests that lower mesenteric weight does not result in significant understaging.

An interesting point raised by this study is the role of mesenteric weight in assessing adequacy of pathological examination. The CAP guideline of a 12 node minimum does not account for differences in mesenteric weight. In our study, both sites had relatively equal lymph node recovery rates per 100 g of mesentery for both right and left colon. We propose that colorectal lymph node minimums should be correlated with mesenteric weight. An acceptable lymph node recovery number would be 6 nodes per 100 g. The results of this study suggest that a change in pathological practice will be required. Weighing of the mesentery should be carried out on an on-going basis. In addition, special care should be taken that the mesentery be stripped from the colonic wall in a standardized fashion to ensure complete nodal recovery.

VII.5 Conclusions

In conclusion, we have undertaken a rigorous study of colorectal carcinoma lymph node recovery in two WRHA institutions. We have assessed diligence of pathological technique, controlling for differences in the surgical specimen by utilizing

mesenteric weight. We conclude that differences in lymph node recovery between the two sites are entirely due to differences in the mesenteric weight, and that pathologic technique is superior to literature averages at both sites. We recommend that surgical technique be investigated as a possible cause for low node recovery at TH; we note that there is no evidence of clinico-pathologic understaging in this small study. We recommend that minimum lymph node recovery standards account for mesenteric weight and that mesenteric weight be a routine component of pathologic evaluation in all colorectal resection specimens.

VIII. TABLES

VIII.1 TNM Designations

T - PRIMARY TUMOR	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ: intraepithelial or invasion of lamina propria
T1	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades through muscularis propria into subserosa or into non-peritonealized pericolic or perirectal tissues
T4	Tumor directly invades other organs and structures and/or perforates visceral peritoneum

**Adopted from the TNM staging manual*

N – REGIONAL LYMPH NODES	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1 to 3 regional lymph nodes
N2	Metastasis in 4 or more regional lymph nodes

** Adopted from the TNM staging manual*

M – DISTANT METASTASIS	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

** Adopted from the TNM staging manual*

VIII.2 TNM Stage Groupings

STAGE	TUMOR	NODE	METASTASIS
Stage 0	Tis	N0	M0
Stage I	T1, T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T4	N0	M0
Stage IIIA	T1, T2	N1	M0
Stage IIIB	T3, T4	N1	M0
Stage IIIC	Any T	N2	M0
Stage IV	Any T	Any N	M1

* *Adopted from the TNM staging manual*

VIII.3 Results Chart

PARAMETER	Community Hospital [Left]	Community Hospital [Right]	Community Hospital [Combined]	Teaching Hospital [Left]	Teaching Hospital [Right]	Teaching Hospital [Combined]
Dates specimens collected	-	-	Oct 25 2002- Apr 6 2004	-	-	Nov 5 2003- Nov 16 2004
Average Age	68.9	72.9	71.0	68.1	74.3	70.8
Male:Female ratio	16:16	18:17	34:33	9:8	10:4	19:12
Average weight [g]	317	325.2	321.4	135.3	169	150.5
Range of weight [g]	32-1064	63-1078	-	11-350	45-726	-
Average length [cm]	25.6	26.8	26.2	22.5	18.2	20.5
Range of length [cm]	7.9-93	6.5-103	-	8-64.5	7-30	-
TOTAL LYMPH NODES						
Average No.	21.3	21.5	21.4	12.4	13.3	12.8
Range	2-44	2-45	-	1-67	4-22	-
Median	20.5	20	20.5	9	13.5	12
No. lymph nodes per 100g	6.7	6.6	6.7	9.1	7.8	8.5
No. cases with <12 nodes / Total cases	10/34 (29.4)	7/38 (18.4)	17/72 (23.6)	11/17 (64.6)	5/14 (35.7)	16/31 (51.6)
NO. NODES PER TOTAL						
size < 0.5 cm	502/723 (69.4)	516/817 (63.5)	1018/1540 (66.1)	183/210 (87.1)	109/186 (58.6)	292/396 (73.7)
size < 0.3 cm	240/723 (33.2)	213/817 (26.1)	453/1540 (29.4)	98/210 (46.7)	44/186 (23.7)	142/396 (35.9)
size < 0.2 cm	56/723 (7.8)	53/817 (6.5)	109/1540 (7.1)	34/210 (16.2)	15/186 (8.1)	49/396 (12.4)

POSITIVE LYMPH NODES						
Average No.	4.2	4.2	4.2	2.4	3.5	3.1
Range	1-24	1-16	-	1-4	1-7	-
No. cases with positive nodes / Total cases	14/34 (41.2)	18/38 (47.4)	32/72 (44.4)	5/17 (29.4)	8/14 (57.1)	13/31 (41.9)
No. positive nodes/ Total nodes	59/723 (8.2)	75/817 (9.2)	134/1540 (8.7)	12/210 (5.71)	28/186 (15.1)	40/396 (10.1)
Incidence of metastasis in nodes:						
<5 mm	29/59 (49.2)	21/75 (28.0)	50/134 (37.3)	8/12 (66.7)	11/28 (39.3)	19/40 (47.5)
<3 mm	10/59 (16.9)	5/75 (6.7)	15/134 (11.2)	3/12 (25.0)	3/28 (10.7)	6/40 (15.0)

* Bracketed values indicate percentages

VIII.4 Statistical Analysis

Comparison	Weight [g]	Total Lymph Node Count	Nodes per 100g	% total nodes < 5mm	% total nodes < 3mm	% positive nodes
CH vs TH combined	0.0002 *	0.0004 *	NS	NS	NS	0.9341
CH vs TH right	0.0039 *	0.0304 *	NS	(0.07)	NS	-
CH vs TH left	0.0249 *	0.0059 *	NS	NS	NS	-
Right vs Left TH	-	-	NS	0.0012 *	0.029 *	-
Right vs Left CH	-	-	NS	0.0114 *	0.0372 *	-
	UTT	UTT	MW	MW	MW	UTT

Statistical tests: MannWhitney U-test (MW), Unpaired T-test (UTT)

* *significant values*
NS – not significant
Bracketed values indicate borderline significance

IX. FIGURES

IX.1 Lymph node recovery

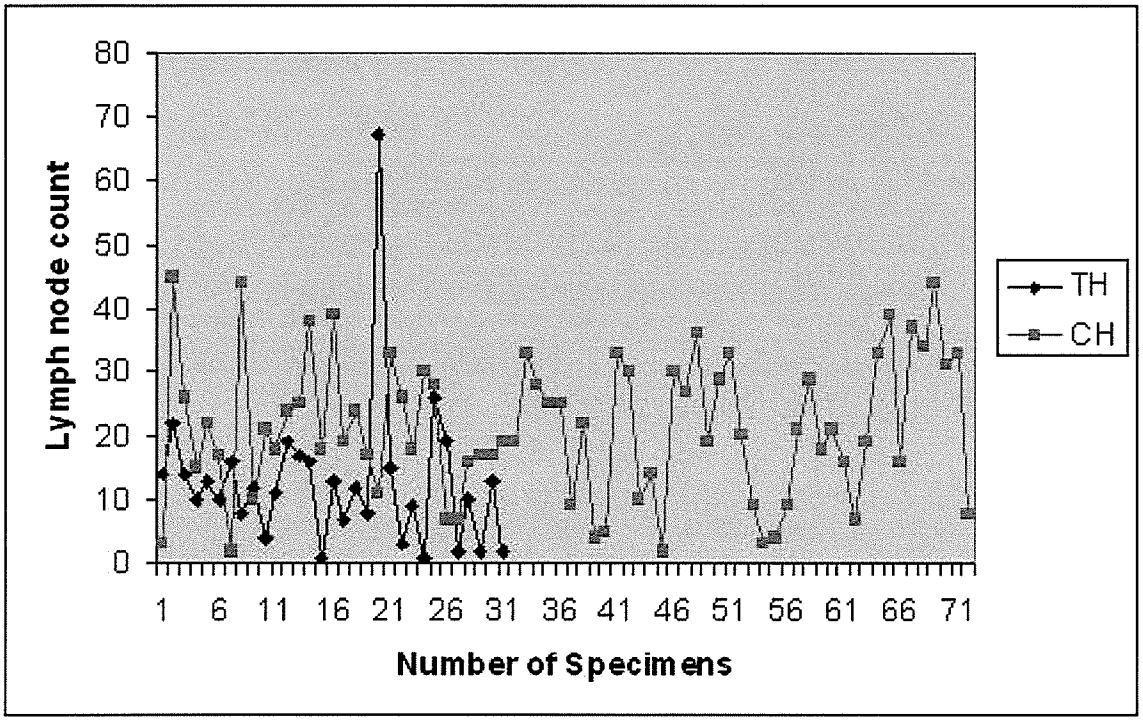

Fig IX.1: Lymph node recovery. Number of lymph nodes recovered at CH (n=32) and at TH (n=72). Lymph node counts for right and left side at both TH and CH was pooled. The average number of lymph nodes recovered at CH was 21.4 compared to an average of 12.8 at TH. The difference between average lymph node count at the two sites was statistically significant with P=0.0004.

IX.2 Percentage of cases with less than 12 nodes recovered

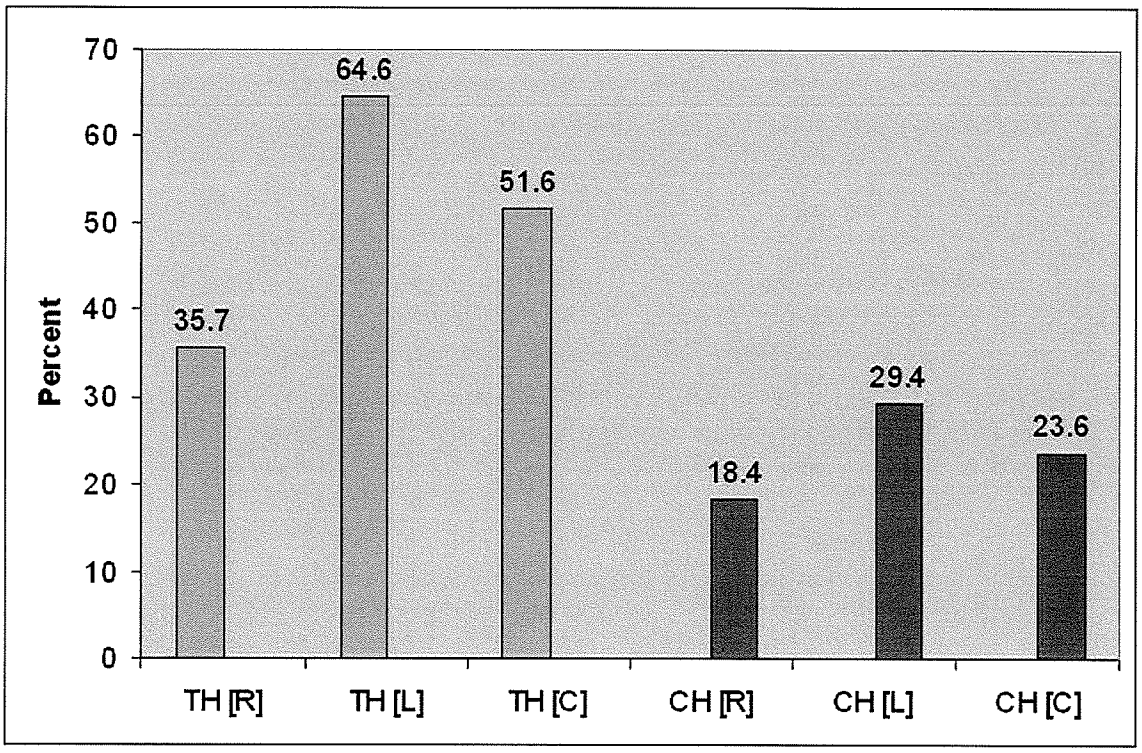

Fig IX.2: Percentage of total cases with lymph node recoveries less than 12. CAP guidelines mandate a minimum lymph node recovery of 12 in colonic adenocarcinoma cases. Proportion of total cases with a suboptimal lymph node recovery was determined for right sided colon resections [R], left sided colon resections [L], and for the pooled data [C] at TH and CH.

IX.3 Small lymph node recovery, <5mm

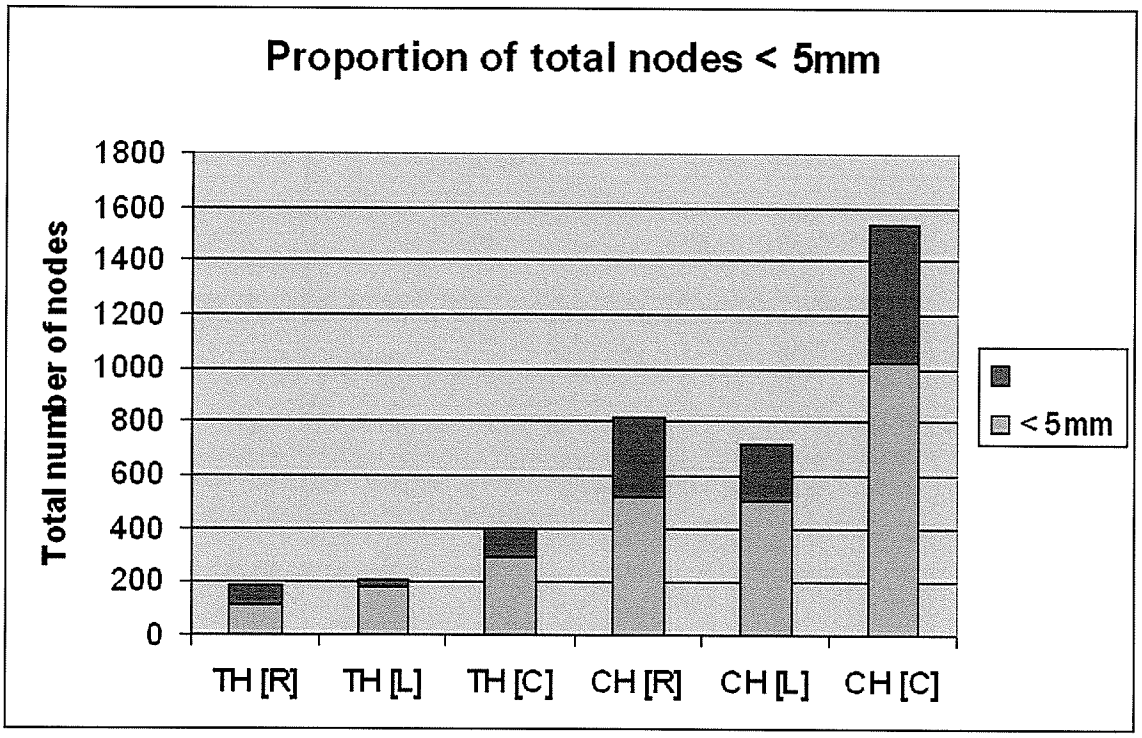

Fig IX.3: Proportion of recovered lymph nodes measuring less than 5 mm. Small node recovery has been established as a parameter for measuring the quality of a lymph node dissection. The proportion of total lymph nodes found which measure less than 5 mm in greatest dimension was determined. Data is expressed as right sided resections[R], left sided resections [L], and pooled data [C] at both TH and CH. The percentage of recovered nodes <5mm are as follows: TH[R] 58.6, TH[L] 87.1, TH[C] 73.7, CH[R] 63.5, CH[L] 69.4, CH[C] 66.1. Statistical significance was found within TH and CH between left and right sides (P=0.0012 and P=0.0114 respectively).

IX.4 Small lymph node recovery, <3mm

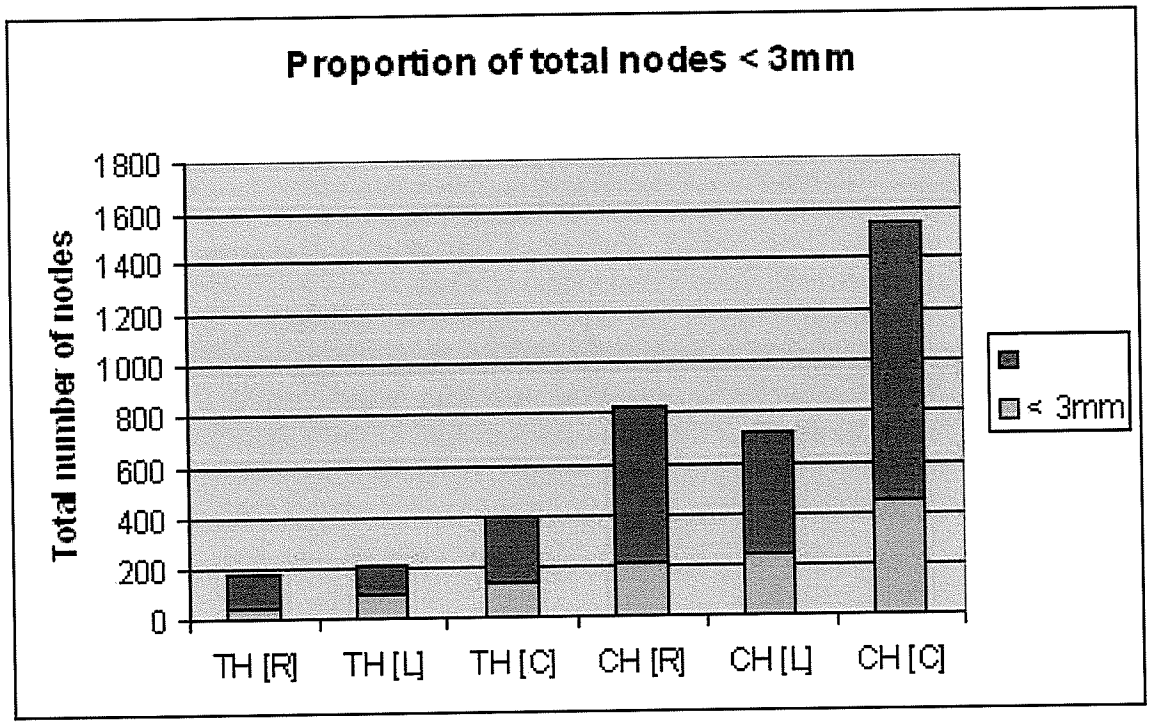

Fig IX.4: Proportion of recovered lymph nodes measuring less than 3mm: Small node recovery has been established as a parameter for measuring the quality of a lymph node dissection. The proportion of total lymph nodes found which measure less than 3 mm in greatest dimension was determined. Data is expressed as right sided resections[R], left sided resections [L], and pooled data [C] at both TH and CH. The percentage of recovered nodes <3mm are as follows: TH[R] 23.7, TH[L] 46.7, TH[C] 35.9, CH[R] 26.1, CH[L] 33.2, CH[C] 29.4. Statistical significance was found within TH and CH between left and right sides (P=0.029 and P=0.0372 respectively).

IX.5 Mesenteric weight at TH vs CH

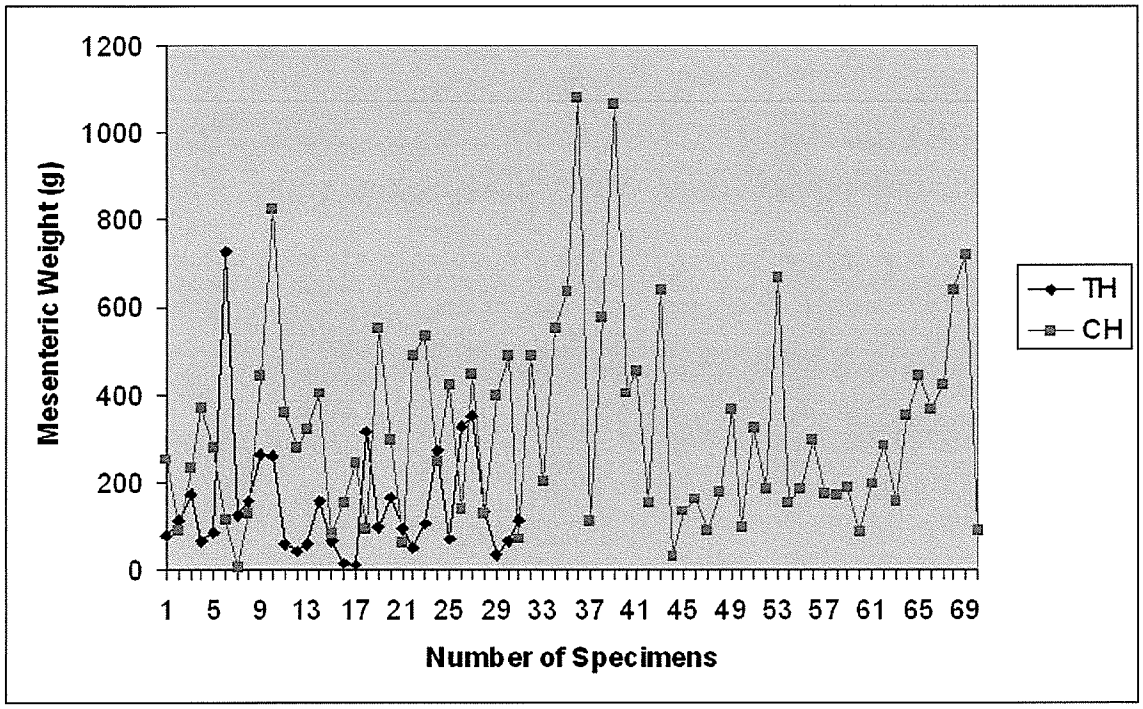

Fig IX.5: Mesenteric weight. Mesenteric weight at CH (n=31) and at TH (n=69). Mesenteric weight for right and left side at both TH and CH was pooled. The average mesenteric weight at CH was 321.4 g compared to an average of 150.5 g at TH. The difference between combined mesenteric weight at the two sites was statistically significant with P=0.0002.

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