

Retrospective analysis of resected primary colorectal cancer revealed no correlation between node harvest and node involvement

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Abstract

Objective: To analyze the correlation between lymph nodes harvest (LNH) and lymph nodes involvement (LNI).

Methods: A retrospective analysis was done from January 2002 - August 2008 (6.5 years). The data was obtained from medical records, pathology and radiology. The patients with primary colorectal carcinoma (CRC) including synchronous or metachronous cancer, were included. These patients were treated with curative or palliative intent. Exclusion criteria was recurrent colorectal cancer, cancer not operated, cancer not resected (stoma-only, open-close) and endomucosal resection. LNH and LNI were obtained. The data was analyzed and also compared with the literature and the national audit.

Results: There were 177 resections (mean=28±3 per annum). Male to female ratio was 0.9:1 and median age was 71 years. There were 112 (63.3%) colonic and 65 (36.7%) rectal cancers. There were 14 Anterior-posterior resections (APRs) (21.5% of all rectal resections). Eighty four percent of resections were elective (OR=2.2 p=0.003 compared to the national audit). Metastasis was found in 14.6% at presentation. Adenocarcinoma (not otherwise specified) NOS constituted 94% of all histology results. Median lymph node harvest was 12 (mean=13.4 p=0.08). There was no significant LNH-LNI correlation (r=0.17 p=0.02). Survival figures for stages I-III CRC revealed 3-year disease-free survival of 82% (all-stage=69%).

Conclusion: LNI as a function of tumour and host behaviour is of prognostic significance whereas LNH may be a quality assurance (QA) tool.

Keywords: Lymph nodes, Retrospective analysis, Colorectal carcinoma, Anterior-posterior resections, Adenocarcinoma (JPMA 61: 1202; 2011).

Introduction

Colorectal Cancer (CRC) remains a complex disease with a major health burden throughout the world. Although, the incidence and mortality are on a slow decline, it still remains third biggest cause of cancer-related mortality in 2008.¹

In last two decades the prognosis of CRC has improved due to development of better cytotoxic and biological therapies but the prognosis remains a function of clinical and histopathologic stage of the colon cancer at diagnosis.² Recent AJCC guidelines (American Joint Committee of Cancer) highlighted several prognostic factors including standard pathological feature such as depth of bowel wall penetration (T), number of loco-regional lymph nodes involved (N) and presence of extra-colonic metastases (M). It is a common belief that there is a strong co-relation between number of harvested lymph nodes (LNH), histological grade, and evidence of lymphovascular and perineural invasion.³

With growing evidence, it is now clearly

understood that there are several clinical and biological factors that can contribute to the prognosis. The important clinical factors include bowel obstruction at diagnosis, ulcerative growth pattern, perforation and elevated Carcinoembryonic antigen (CEA), which all can be associated with poor prognosis. We also know that molecular prognostic factors such as p53, loss of heterozygosity for 18q, Epidermal Growth Factor Receptor (EGFR) amplification and Kirsten rat sarcoma viral oncogene homolog (K-RAS) mutations can all have prognostic implications.⁴

In the light of the recent developments, there is a better understanding about the tumour biology and this is complimented by our clinical observation that the tumour prognosis is primarily driven by above factors rather than a co-relation between LNH and LNI. Therefore the aim of this study was to analyze the relationship between the number LNH and the number of lymph nodes involved LNI, at the histological examination of the specimens of resected primary colorectal cancer at our unit.⁵

Patients and Methods

A retrospective analysis of all patients undergoing resection of primary colorectal cancer (CRC) was carried out at the departments of surgery at a district general hospital and of pathology at a regional teaching institution, both in Northern Ireland UK. The study period was January 2002 to August 2008 inclusive (6.5yrs). The information was obtained from the clinical records and from the department of pathology. The patient inclusion criteria were resection of primary CRC (curative or palliative intent) including synchronous or metachronous cancer. Exclusion criteria were recurrent CRC, cancer not operated, cancer not resected (stoma-only, open-close) and endomucosal resection. Recorded information included anonymised demographic details, elective / urgent status, anatomical location of the cancer, type of resection, mesorectal excision, histological type of the cancer, longitudinal resection margin (LRM), circumferential resection margin (CRM), lymphovascular invasion (LVI), extramural venous permeation (EMVP), lymph node harvest (LNH), lymph node involvement (LNI), pathological (p) TNM stage and R level of resection (R0 =margins microscopically clear, R1 =microscopically involved and R2 =gross residual disease). All data were recorded on Microsoft Excel 2005 summary sheets.

Statistical analysis was done by a one-sample t-test, used for LNH by using the National Bowel Cancer Audit Project (NBOCAP) value (of median harvest of 12 lymph nodes) as the 'hypothetical mean'. Spearman Rank test was applied for LNH-LNI correlation (p value at 0.05) was considered significant.

Results

Over the 6.5-year study period, 177 resections for primary CRC were performed. Mean number of resections per annum was 28 ± 3 . There were 112 (63.3%) colonic and 65 (36.7%) rectal cancers. M: F ratio was 0.9:1. Median age was 71 years for colonic and 69.5years for rectal cancers.

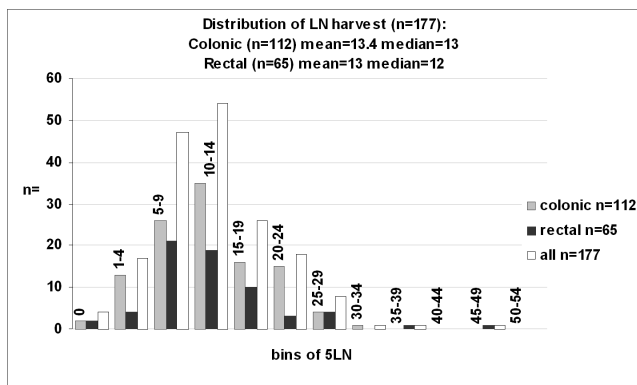


Figure-1: Distribution of Lymph Node Harvest in colonic, in rectal and in all-inclusive resection specimens.

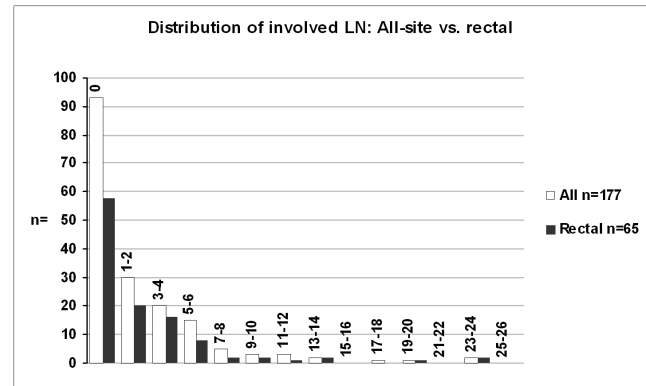


Figure-2: Distribution of Lymph Node Involvement in all-inclusive and in specifically rectal resection specimens.

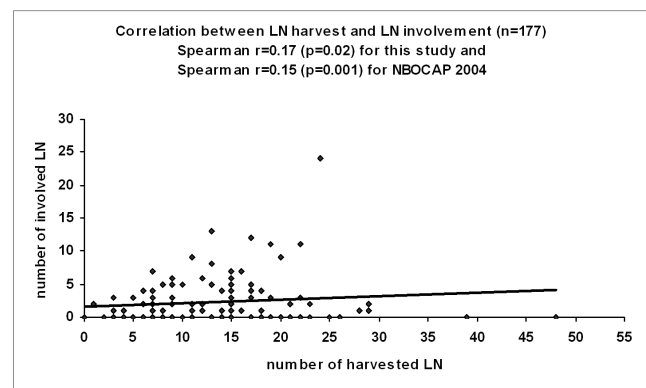


Figure-3: The scatter plot revealed wide dispersal around the regression line. Since the small relationship between LNH and LNI is supposedly linear, the regression coefficient is equivalent to correlation coefficient.

Eighty eight percent of resections were elective (OR=2.2 RR=1.14 $p=0.003$ compared to the UK national audit).⁶ Adenocarcinoma constituted 94% of all histology results (5% mucinous and 1% signet ring). It was well differentiated in 2.8% specimens, moderately differentiated in 85.2% and poorly differentiated in 12%. Median CRM was 7.5mm (Interquartile range (IQR)=1.5-13 range=0-35). The CRM involvement was 12.7% for all CRC and 16% for rectal cancers. The LRM involvement was 1.5%. Median overall LNH was 12 (IQR=8-17, range 0-48). Mean LNH was 13 (SD=7 SEM=0.65 mode=9). The p-value was 0.08 when compared to the recommended LNH of 12. Median LNH for rectal cancers was 12 and was 13 for colonic cancer. There were 14 (21.5%) APRs compared to 51 (78.5%) sphincter-saving operations from a total of 65 rectal resections. Eighty four percent of resections were R0. The histological stage-wise distribution was Stage-I/II=43%, III=38%, IV=17.6%. Missing data was noted for 1.4%. Nodal status revealed pN0=50%, pN1=26.4% and pN2=23.6%. The 30-day all-cause mortality was 4.3%.

Actuarial survival curve demonstrated 14.6% chance of metastasis at presentation, all-stage 3-year disease-free survival (DFS) of 69% and of 82% for stages I-III (Tany Nany M0). Carcinoembryonic antigen (CEA) relapse as a marker of disease recurrence (available for n=125) revealed 3-year DFS=68%.

When correlation was determined between LNH and lymph node involvement, it revealed a low correlation ($r=0.17$ $p=0.02$) (Figs 1-3). When the national audit calculated the same relationship among its much larger sample the results were the same ($r=0.15$ $p=0.001$).

Discussion

Royal College of Pathologists 2nd edition Colorectal Cancer Report Dataset specifies pathological standards such as mean LNH of 12, EMVP to be identified in >25% of cases, and, pT4b (tumour invading into adjacent organs) serosal disease in >10% and >20% of rectal and colonic cancers respectively.⁷ Macroscopic assessment of the plane of surgical excision (TME) is done in all relevant cases. In this study the confounding was minimal as age, gender, social class and the time of the day were similar. It was also not contaminated by recurrent or open-close operations.

Lymphadenectomy in colorectal cancer is believed to be a critical component concerning prognosis and survival of patients and that the number of positive lymph nodes remains the best discriminator of survival⁸ as is true in any GI malignancy.⁹ A recent study has suggested a similar benefit in advanced lower rectal cancer patients having LNI in the lateral pelvic area who are likely to receive prognostic benefit from lymphadenectomy. The role of preoperative computed tomography (CT) for prediction of lateral node involvement in patients with low rectal cancer has also been assessed in a recent study¹⁰ and these patients might benefit from extended lateral node dissection. Another interesting find in a recent study¹¹ is that the number of negative nodes is also an important independent prognostic factor for patients with stage IIIB and IIIC colon cancer.

There are a number of factors which influence number of lymph node harvest in colorectal surgery such as age, sex, Duke Stage, operative urgency, pre-operative radiotherapy, inflammatory response and LNH decreases slightly as the CRC goes distally.^{12,13} The Association of Coloproctologists of Great Britain and Ireland have developed an ACPGBI LN Harvest Model to predict the number of lymph node harvest in patients undergoing resectional surgery for colorectal cancer.^{13,14} Another medium sized prospective study showed that the overall lymph node harvest, varied according to the reporting pathologist but not operating surgeon and also that as the

lymph node harvest increased to 15 per patient, the probability of identifying a metastatic node increased. A recent study¹⁵ of more than 1500 patients concluded that ascertainment of Dukes' stage C cases was related to number of lymph nodes examined, with optimal ascertainment levels when at least 10 and fewer than 15 nodes were examined.

Our study shows conflicting evidence and revealed a low correlation ($r=0.159$ $p=0.06$) between lymph node harvest and lymph node involvement and was statistically insignificant. Another large cohort study¹⁶ of more than 30,000 patients concluded that the frequency of finding a single positive node or multiple positive nodes was nearly identical and independent of the number examined, thus raising real questions about the value and importance of examining a large number of lymph nodes and also concluded that the number of lymph nodes examined following colectomy for colon cancer was not associated with staging, use of adjuvant chemotherapy, or patient survival.

Conclusion

Lymph node involvement as a function of tumour and host behaviour is of prognostic significance whereas lymph node harvest may be a marker of 'pathologist's diligence' at the histological examination and therefore a quality assurance (QA) tool. Current TNM rules recommend that a regional lymphadenectomy for CRC includes a minimum of 12 lymph nodes.

Among node-negative patients, the departments of pathology with the lowest median number of examined nodes yielded the worst patient survival, reflecting that this group of node-negative patients contained N1 patients wrongly staged as N0. Inclusion of the number of lymph nodes examined decreased the differences between the departments. This means that a reduction in mortality among these node-negative patients could be achieved by increasing the number of lymph nodes examined in the departments with the lowest numbers. The difference in survival among node-positive patients after adjustment for the number of nodes examined indicated that other relevant clinical features differ between institutions, in addition to the determinants we assessed in our analyses.

References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer Clin* 2011; 61: 69-90.
2. Kohler BA, Ward E, McCarthy BJ, Schymura MJ, Ries LA, Ehemann C, Annual Report to the Nation on the Status of Cancer, 1975-2007, Featuring Tumors of the Brain and Other Nervous System. *J Natl Cancer Inst* 2011; 103: 714-36.
3. AJCC Cancer Staging Manual. 7th edition. Edge SB, Byrd DR, Compton CC, et al (Eds). New York: Springer 2010; pp 143.
4. Compton CC, Fielding LP, Burgart LJ, Conley B, Cooper HS, Hamilton

- SR, et al. Prognostic factors in colorectal cancer: College of American Pathologists Consensus Statement 1999. *Arch Pathol Lab Med* 2000; 124: 979-94.
5. Berger AC, Sigurdson ER, LeVoyer T, Hanlon A, Mayer RJ, Macdonald JS, et al. Colon cancer survival is associated with decreasing ratio of metastatic to examined lymph nodes. *J Clin Oncol* 2005; 23: 8706-12.
 6. Tekkis PP, Smith JJ, Heriot AG, Darzi AW, Thompson MR, Stamatakis JD, et al. A national study on lymph node retrieval in resectional surgery for colorectal cancer. *Dis. colon rectum* 2006; 49: 1673-83.
 7. Williams G, Quirke P, Shepherd N. Dataset for colorectal cancer (2nd edition). London: The Royal College of Pathologists 2007.
 8. Cohen AM, Tremitterra S, Candela F, Thaler HT, Sigurdson ER. Prognosis of node-positive colon cancer. *Cancer* 1991; 67: 1859-61.
 9. Wong SL, Ji H, Hollenbeck BK, Morris AM, Baser O, Brikmeyer JD. Hospital lymph node examination rates and survival after resection for colon cancer. *JAMA* 2007; 298: 2149-54.
 10. Lowenfels AB, Wong SL, Hong J, Hollenbeck BK. Does the number of lymph nodes examined affect survival in colon cancers. *JAMA* 2007; 298: 2149-54.
 11. Johnston PM, Porter GA, Ricciardi R, Baxter NN. "Increasing negative lymph node count is independently associated with improved long-term survival in stage IIIB and IIIC colon cancer". *J Clin Oncol* 2006; 24: 3570-5.
 12. Tekkis Paris P, Smith JJ, Heriot AG, Thompson MR, Stamatakis. Association of Coloproctology of Great Britain and Ireland "A national study on lymph node retrieval in resectional surgery for colorectal cancer": *Dis Colon Rectum* 2008; 51:366-7.
 13. Wind J, Lagarde SM, Ten Kate FJ, Ubbink DT, Bemelman WA, van Lanschot JJ. A systematic review on the significance of extra capsular lymph node involvement in gastrointestinal malignancies. *Eur J S Oncology* 2007; 33: 401-8.
 14. Yano H, Saito Y, Takeshita E, Miyake O, Ishizuka N. Prediction of lateral pelvic node involvement in low rectal cancer by conventional computed tomography. *Br J Surg* 2007; 94: 1014-9.
 15. Chang GJ, Rodriguez-Bigas MA, Skibber JM, Moyer VA. Lymph node evaluation and survival after curative resection of colon cancer: systematic review. *J Natl Cancer Inst* 2007; 99: 433-41.
 16. Pheby DF, Levine DF, Pitcher RW, Shepherd NA. Lymph node harvest directly influence the staging of colorectal cancer: evidence from a regional audit. *J Clin Pathol* 2004; 57: 43-7.
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