

Retrospective Study on the Prognostic Significance of Lymph Node Data Post Colorectal Cancer Resection

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Background

Lymph node data regarding the number of lymph nodes resected and studied have been found in previous studies to have prognostic value in patients diagnosed with colorectal cancer (CRC). CRC patients who underwent colorectal resections at Malta's main hospital, Mater Dei Hospital (MDH), between 2008 and 2011 were selected to assess the prognostic value of such data.

Methods

The Surgery Department compiled patients who underwent colorectal resections at Mater Dei. Histopathology reports were obtained from MDH's intranet through iSoft's iClinical Manager (iCM) and physical files. Microsoft Excel and IBM SPSS statistics were used to compile and analyse the data.

Results

The number of lymph nodes resected showed a mildly significant correlation with overall survival with the Area Under the Receiver Operating Characteristic curve (AUROC) of 0.629 (CI – 95%, $p = 0.008$) in Stage II CRC patients. 13 lymph nodes were found to be the best cutoff below which there are risks of under-staging of Stage II patients and decreased survival. LNR and number of positive lymph nodes showed more significant correlation with overall survival with AUROC 0.739 (C.I. 95%; $p = <0.0001$) and 0.726 (C.I. 95%; $p = <0.0001$) respectively. Both LNR and number of positive lymph nodes correlated significantly with rates of new metastasis with AUROC 0.735 (C.I. = 95%; $p = <0.0001$) and 0.733 (C.I. = 95%; $p = <0.0001$), respectively. The best cutoff point for LNR was 8% in both cases.

Conclusion

Adequate lymph node exploration and removal are encouraged to avoid under-staging of disease that can potentially occur in Stage II patients with less than 12 lymph nodes resected. Lymph Node Ratio (LNR) provides a better overall picture of lymph node infiltration than N stage and the number of positive lymph nodes.

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Colorectal cancer (CRC) is the second most common cause of cancer death in Malta, topped by lung cancer in males and breast cancer in females.

According to studies, the most common histological presentation of CRC is adenocarcinoma, found in 90% of cases.¹ Approximately 75% of CRC patients will present with potentially curable disease that is treated by surgical resection. According to guidelines released by the American Society of Colon and Rectal Surgeons (ASCRS), surgical treatment of colon disease (from the caecum to rectosigmoid) should include resection of the affected segment with the mesentery containing lymph nodes and blood vessels supplying the area and any infiltrated organs undergoing en bloc resection. Moreover, any rectal cancer should be removed ideally by radical excisions with total mesorectal excision for cancers affecting the middle and lower thirds of the rectum and tumour-specific mesorectal excision for disease in the upper third. In addition, draining lymph nodes need to be removed up to the origin of the primary blood supply to that segment of the bowel.^{2,3}

This study aims to analyse local data on circumferential resection margins (CRM) and lymph node resection in CRC patients undergoing surgical resections by following a local cohort between 2008 and 2011 of 598 patients documented in Malta's main hospital, Mater Dei Hospital. Screening via Faecal Immunochemical Testing (FIT) was introduced in 2012, a year after this cohort was treated.

METHODOLOGY

Study Design

Approval and collection of raw data

Data on all patients affected by CRC between 2008 and 2011 were provided by the Surgery Department. Permission to use the data, including patients' online and physical files and notes, was certified by the Data Protection branch at Mater Dei before data was accessed. The study received ethical approval by the Maltese Health Ethics Committee (HEC).

Pathology Report Template

Each patient had to have at least one report issued when the primary disease was removed. Some also had other histopathology reports from margin

correction surgeries or surgeries to excise local recurrences. Reports used in this study had to be detailed and organised as suggested by The Royal College of Pathologists UK.⁴ Patients with incomplete pathology reports had to be excluded at specific parts of the study or completely, depending on the data available.

Tools used for data collection and analysis

- iSoft's iClinical Manager (iCM) - used in all hospitals and public health centres in Malta. Almost all data on histology and scanning results were collected using iCM.
- Microsoft Excel - spreadsheet software used to compile the data and present it graphically.
- International Business Machines Corporation (IBM®) Statistical Package for the Social Sciences (SPSS®) (version 25) was used to work on all statistics
- Physical files were occasionally used to confirm findings during colonoscopy and surgery, incidence dates and dates of death

Data Collected for the study

During the data collection process, the data were cross-checked several times by data collectors to avoid mistakes. A fixed census date was chosen on which all mortality and recurrence data were checked for the last time.

Patients were grouped by stage according to AJCC 7th Edition Guidelines for CRC. Sub-stages were grouped together to simplify the data and allow for more consistent results; stages IIA–IIC were grouped as Stage II, stages IIIA–IIIC as Stage III, and stages IVA and IVb as Stage IV.

Exclusion and inclusion criteria

Patients with confirmed colon cancer thus considered for the study were those with explicit mention of adenocarcinoma of colonic origin reported by the pathology department.

The size of cohorts for each year from 2008 to 2011 was 170, 173, 127 and 128, respectively, with a starting cohort of 598 patients. However, the study cohort was reduced to 477 patients after all exclusion criteria were applied.

Patients who did not have surgery done were automatically excluded from the study. Such patients were usually not fit for surgery either because of multiple comorbidities, age or present with a highly invasive disease with several distant metastases. This study aimed to study prognostic patterns of colorectal adenocarcinomas; those with rare histological presentations, mainly mucinous, spindle, undifferentiated and neuroendocrine, had to be excluded from the study.

Patients who died in the first two weeks post-operation mainly due to complications post-operation had to be excluded. Patients lost to follow-up mostly due to change in country of residence, also had to be excluded from the study.

Synchronous tumours are two or more cancers presenting together or within two months. On the other hand, metachronous tumours are two or more cancers presenting more than two months apart.⁵ In this study, patients with synchronous primaries outside the colon and metachronous tumours, colorectal or outside the colon, were excluded. Patients diagnosed with new primaries unrelated to colorectal tissue, such as ovarian, breast, vulval, and prostate diagnosed before or after being operated on, had to be excluded. Patients presenting with a new primary CRC presenting in a different site more

than two months after the other were also omitted. Synchronous colorectal adenocarcinomas were included, with the more invasive disease used for staging and margin data.

The rest of the patients included in the study had appropriate follow-up data either through follow-up outpatients or even presenting again at Mater Dei as emergency cases with repeat scans taken when disease progression was suspected. A total of 477 (80%) patients were eligible and used for this study (Figure 1).

These exclusion and inclusion criteria helped make the study fair and reliable, as shown by similar studies worldwide.

RESULTS

Significance of Non-Modifiable Risk Factors

Out of the 477 patients in the study cohort, 265 (55%) were males, and 212 (45%) were females. 5-year survival between sexes did not change significantly, with males barely having a 3% higher mortality rate in 5 years than females. 57.5% of females lived for more than five years since diagnosis in this cohort, while 54.3% of males made it up to 5-year survival.

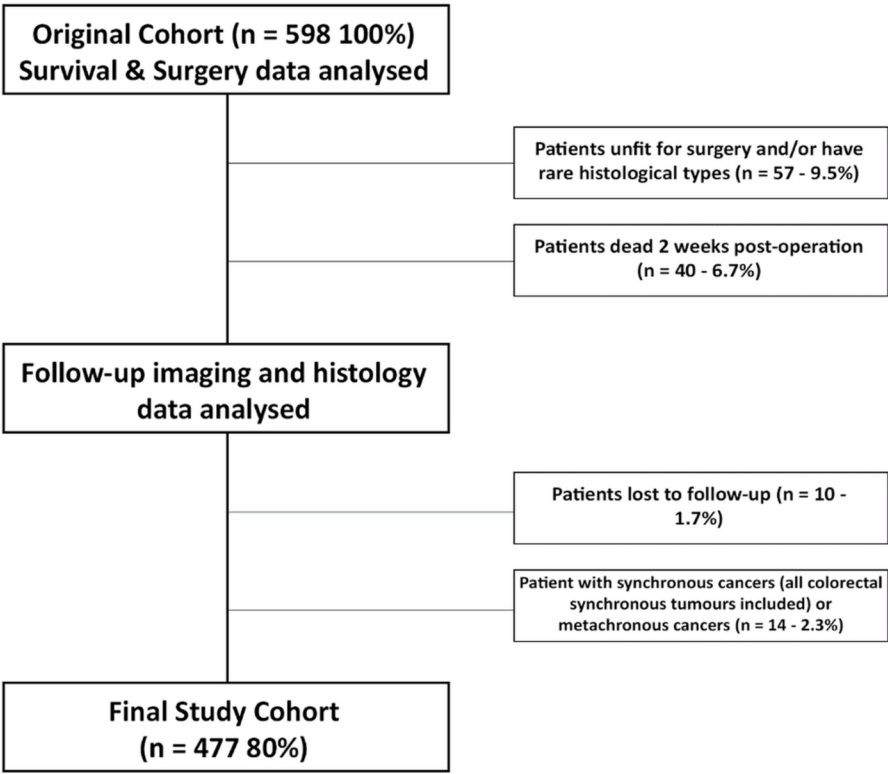


Figure 1 Flow chart of patients' cohort definition with inclusion and exclusion criteria

In this local study, females seem to be diagnosed with CRC younger than males, with around 60% of females presenting before the age of 70. In contrast, most males were diagnosed between ages 70 and 84 but had a higher tendency to present with Stage III or above disease than females (49%).

86 patients (18.0%) presented with stage I disease, 144 patients (30.2%) with Stage II disease, 170 patients (35.6%) with Stage III disease, and 77 patients (16.1%) with Stage IV disease.

52% of the study cohort presented and were operated on quite late with Stage IIIA or above disease, meaning that disease had already invaded at least local lymph nodes by the time they had their resection surgery. The rectum was the most affected site ($n = 138$) in the study cohort, followed by the sigmoid and caecum. Left-sided colon cancer (LSCC) was more common ($n = 181 - 53.4\%$) than right-sided colon cancer (RSCC) ($n = 158 - 46.6\%$). Rates of stage III or above RSCC were, however, approximately the same as LSCC. On the other hand, patients with rectal cancer had significantly lower Stage III or above disease rates than the rest of the colon at 47%.

The younger age group between ages 40 and 54 presented with a higher percentage of advanced disease (Stage III = 42.3%; Stage IV = 17.3%) followed up by patients between ages 70 and 84 (Stage III = 39.7%; Stage IV = 17.5%) than any other age group. As expected, older patients survived poorly post-procedure, with only 48% of patients between the age of 70 and 84 surviving more than five years. Almost 52% of patients older than 85 died within three years of diagnosis.

Significance of Lymph Node Data

Number of positive lymph nodes vs. lymph node ratio (LNR) as prognostic factors

Patients with right-sided CRC, mainly in the caecum and ascending colon (30% and 25% respectively), presented more frequently with N2 staged disease (spread to four or more regional lymph nodes) than those with left-sided disease (average 19%) or rectal cancers (13%). The proportion of N2 disease rose progressively from rectal tumours to left-sided and then right-sided sites. Analysis showed this difference was highly significant (Pearson two-tailed correlation = -0.110 ; $p < 0.0001$).

Overall Survival

Both the number of positive lymph nodes and the lymph-node ratio (LNR) were highly correlated with overall survival (OS). To avoid under-staging, patients with fewer than 12 lymph nodes examined—as recommended by the AJCC—were excluded from this analysis, leaving 305 patients; 172 were excluded.

Survival fell sharply as the number of positive nodes increased. Among patients with no positive lymph nodes, 71% survived beyond five years (with 22% dying within three years and 7% between three and five years). For those with one positive node, the proportion surviving more than five years fell to 52.5%, and when 2–3 nodes were positive only 30.6% lived beyond five years. In cases with more than seven positive nodes only 14.3% reached five-year survival, with 76.2% dying within three years.

Low lymph-node ratio values were associated with significantly better outcomes: 73.9% of patients with an LNR below 0.07 survived beyond five years (18.9% died within three years and 7.2% between three and five years). When the LNR was 0.08–0.25, only 40.0% survived beyond five years, and at 0.26–0.50 the five-year survival rate was 51.7%. Very high LNR (>0.5) corresponded to only 3.8% of patients surviving beyond five years and 92.3% dying within three years.

ROC analysis confirms the correlation of both the number of positive lymph nodes and LNR with 5-year OS. However, by comparison, LNR was found to correlate better with AUROC correlation of 0.739 (CI 95%; $p = <0.0001$) versus of 0.726 (CI 95%; $p = <0.0001$) when number of positive lymph nodes only was considered. Such analysis also suggests that the best cut-off for a favourable 5-year overall survival is two or fewer positive lymph nodes or a lymph node ratio of 8% or less (sensitivity 60%, specificity 80%).

Results were used for Kaplan–Meier analysis highlighting steeper declines in overall survival with increasing numbers of positive lymph nodes or higher LNR values (**Figure 2**).

Metastasis-Free Survival (MFS)

Distant metastasis within five years also increased markedly with higher nodal burden. Only 15.9% of patients with no positive nodes developed metastases, but this rose to 30.0% with one positive

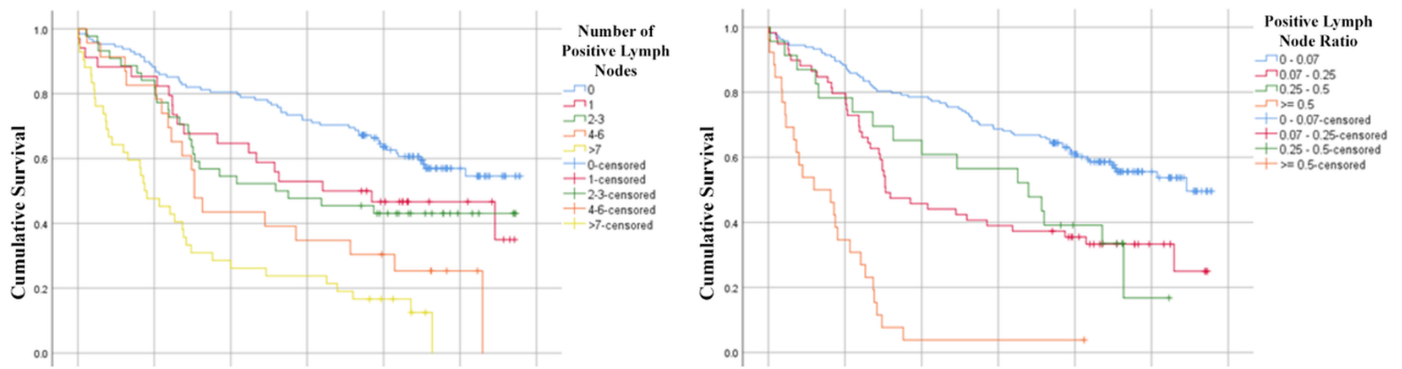


Figure 2 Kaplan Meier Graphs on OS comparing the number of positive lymph nodes (a) and LNR (b)

node, 36.7% for 2–3 positive nodes, 34.5% for 4–6 positive nodes and 54.8% when more than seven nodes were positive. A similar pattern was observed with the lymph-node ratio: 19.4% of patients with an LNR below 0.07 developed metastasis compared with 34.3% for LNR 0.08–0.25, 41.4% for 0.26–0.50 and 57.7% for LNR above 0.5.

A correlation was recommended with ROC analysis for the number of positive lymph nodes and LNR vs. MFS with AUROC of 0.733 (CI = 95%; $p = <0.0001$) and 0.735 (CI = 95%; $p = <0.0001$) respectively. Coordinates of the ROC curves showed that three positive nodes gave a sensitivity of 86% and specificity of 48%, whereas an LNR of 8% gave a sensitivity of 80% and specificity of 57% for predicting five-year metastasis-free survival

Kaplan–Meier curves of metastasis-free survival similarly demonstrated that higher positive node counts or LNR values were associated with earlier metastasis (**Figure 3**).

Number of lymph nodes resected as a prognostic factor

When all the study cohort was included to research the prognostic value of the number of lymph nodes resected, no correlation could be confirmed. The cohort was thus divided according to AJCC stages testing each one of them for significant correlations.

The number of lymph nodes resected in patients with Stage II disease was then found to influence overall survival. No significant correlation could be found in any other stage tested separately.

Five-year survival in Stage II disease patients improved with a higher number of nodes examined. In this cohort 46.7% of patients with only 0–5 lymph nodes resected survived beyond five years; the rate rose to 62.5% when 5–10 nodes were resected, 68.8% for 11–15 nodes and 77.6% when more than 16 nodes were removed. Correspondingly, the proportion dying within three years fell from 34.4% with 5–10 nodes to 16.7% with 11–15 nodes and 20.4% with more than 16 nodes.

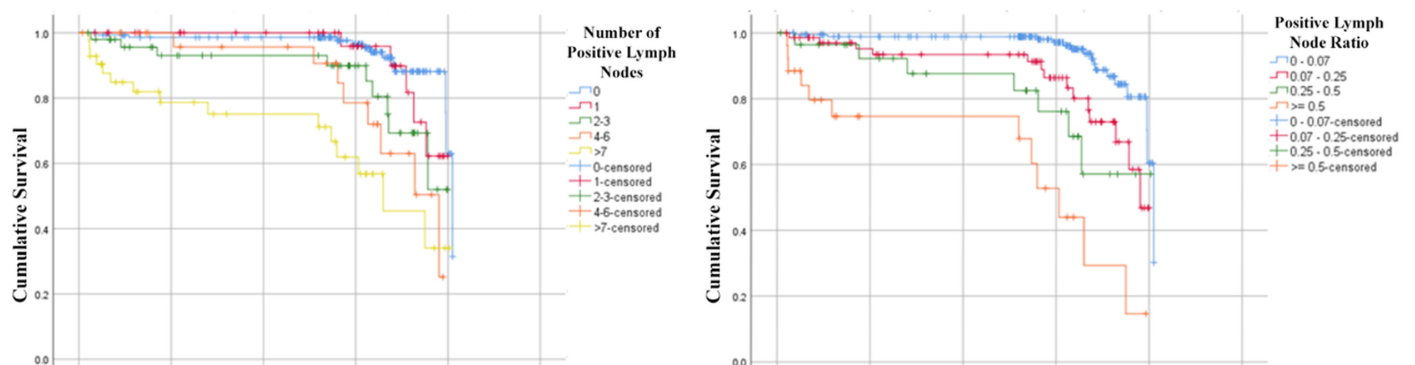


Figure 3 Kaplan Meier Graphs on New Distal Metastasis Survival rates comparing the number of positive lymph nodes (a) and LNR (b)

This study aimed to correctly measure how lymph node data post-surgery can properly predict OS and oncological outcomes.

The main limitation in data collection was that most histopathology reports failed to mention where lymph nodes were removed and which of the lymph nodes removed were positive. The Japanese Society for Cancer of the Colon and Rectum classification divides N stage according to the most distal vascular arcade with associated positive lymph nodes. Studies have shown that lymph nodes distal to the primary lesion arcade, and proximal to main vessels, carry poorer the prognosis. Such a classification was a better prognostic indicator than TNM staging itself.⁶ Unfortunately, due to the lack of localising data of the nodes removed, such a classification could not be applied locally.

The study aimed to tackle whether an ideal number of lymph nodes should be resected and serve as a reliable prognostic factor. The latest AJCC staging criteria suggest that 12 lymph nodes should be resected and analysed, and these need to be removed with the mesentery and feeding vessels to remove both local and central lymph nodes.⁷ The ASCRS has even recommended this in their latest colon and rectal cancer treatments, especially for N0 staging confirmation in Stage II disease.^{2,3} Local studies showed that 13 lymph nodes seemed to be the best cut off point confirmed through ROC curve studies. The number of lymph nodes resected was found to correlate with OS in Stage II disease mildly, with barely 46% of patients survived for five years when less than five lymph nodes were resected. Local results were similar to extensive studies done in the US that suggested that at least 10 lymph nodes should be resected, with best results noted when more than 15 are resected.⁸

A systematic review done by the Journal of the National Cancer Institute (JNCI) found that 16 out of 17 studies confirmed that the number of lymph nodes resected and studied affects OS. One Italian study increased the mean number of nodes examined from 11.3 ± 5.8 to 29.6 ± 16.7 and reported an 8% increase in five-year overall survival. Another large randomised controlled study done in Italy by Prandi, Lionetto et al confirmed that survival did improve as more lymph nodes were analysed in Stage II colon

cancer. In this study, an 8% improvement in OS was reported when more than 12 lymph nodes were resected in Stage II disease. On the other hand, the same study found that a similar correlation could not be found in Stage III disease suggesting that resection of fewer lymph nodes may potentially lead to under-staging thus not receiving appropriate treatment and follow-up after resection.⁹ In the case of our local study, the increase from 0-5 lymph nodes analysed to 5-10 lymph nodes analysed was enough to increase 5-year OS by 15.8%. However, it needs to be appreciated that only 15 Stage II colorectal patients had less than 5 lymph nodes resected. A more extensive local cohort study would be ideal.

Lymph node ratio (LNR) was used in different studies to compare its prognostic value in CRC with the number of positive lymph nodes and other prognostic factors. This study took the example of similar studies studying LNR and positive lymph node numbers by excluding patients with less than 12 lymph nodes to avoid under-staged patients, who would act as a potential confounding factor and lead to unreliable predictive values [7,8,10,11]. In a study done by Sabbagh, Mauvais et al in France, only stage III colon patients were included and were split into four quartiles; LNR1 below 0.07, LNR2 between 0.07 to 0.25, LNR3 between 0.25 and 0.5 and LNR4 for ratios above 0.5. The results obtained by this study were very similar to the ones obtained in the local study and considered 10% as the best cutoff point compared to 8% in this local study. Both studies showed that statistically, the LNR ratio correlated significantly with OS and DFS.¹⁰

Another study in the US with over 3000 patients suggested a similar cutoff point of less than 8% with a 5-year survival of 86% below such cutoff with improvement in survival with both N1 and N2 staged disease. This study encourages more thorough node dissection to ensure the removal of positive lymph nodes and proper staging, leading to better post-operative treatment.⁸

LNR was consistently found to have a better prognostic value than the number of positive lymph nodes, especially when considering the more extensive AUROC results in OS (0.739 vs 0.726) and MFS (0.735 vs 0.733). These results were similar to recent multinational studies, with a systemic review confirming that LNR serves as a statistically significant prognostic factor than TNM staging.¹²

CONCLUSION

This local study has studied the outcomes of colorectal surgery as influenced by lymph node data. New cut-off points have been suggested that may be included in new local surgical guidelines. The following are some take-home messages:

- Thorough lymph node extraction is encouraged as much as possible, especially suspicious lymph nodes distant to the affected vascular arcade, to avoid missing positive lymph nodes that would lead to incorrect management post-procedure.
- LNR should be given more importance over N staging when it comes to prognosis and

management after resection as it effectively considers the overall picture on the rate of lymphatic infiltration.

This local study could well be the first study publishing in Malta to review the number of lymph nodes resected, LNR, and assess their burden with OS, distant metastasis rates and local recurrence rates. It should encourage more studies on CRCs to be done locally, ideally reviewing patients who had CRC after 2011 and compare results. The aim of upcoming studies should assess whether recent surgical and oncological guidelines, nurse navigators, screening via FIT Testing and fast-tracking systems have improved survival and rates of disease progression.

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