

The Assessment and Evaluation of Factors of Prognostic Significance in the Management of Colorectal Cancer

Factors of prognostic significance in the treatment of CRC

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ABSTRACT

Objective: To evaluate the association of lymph node retrieval, lymph node ratio (LNR) and various other prognostic factors in the management of colorectal cancer (CRC).

Study Design: A retrospective and longitudinal study.

Place and Duration of Study: This study was conducted at the Department of General Surgery Khalifa Gul Nawaz (KGN)MTI Bannu between July 2019 and January 2020.

Materials and Methods: This study was conducted on the data of 450 consecutive patients with colorectal cancer (CRC), admitted to the Department of General surgery KGN MTI Bannu between Jan 2010 and Dec 2014 and who underwent curative resection for colorectal cancer. The data was collected from the clinical charts, computer record and the pathological reports and were reviewed retrospectively and longitudinally for various prognostic factors in the management of CRC. Follow up period was 5 years.

The data were fed to the computer for analysis and calculation of rates, percentages, means and median of variables. Comparisons between variables were assessed for significance by using Pearson chi-square (χ^2) test and Fischer exact test, with the threshold for significance the $p < 0.05$. Kaplan-Meier curves were used to calculate and depict the overall survival in different groups of patients.

Results: A total of 450 patients with colorectal cancer were analyzed. For stage I and stage II or node negative disease, the 5yr survival was 65-70%, declining to 50% for patients with stage III or node positive disease. For Duke stages B and C, there was a significant difference in the overall survival (OS) in patients with < 12 versus > 12 lymph nodes (LNs) retrieved. There was a statistically significant difference in the overall survival (OS), disease free survival (DFS) and recurrence rates in patients with different number of lymph nodes retrieved, the number of lymph nodes with metastases and lymph node ratios (LNRs). Histological subtypes, the surgeon, and the pathologist also played a significant prognostic role in the management of CRC.

Conclusion: Retrieval of > 12 lymph nodes, thorough evaluation of lymph nodes and decreased lymph node ratio have a significant effect on the long term survival and recurrence in the CRC patients.

Key Words: Colorectal cancer (CRC), Lymph nodes numbers (LNs), lymph node ratio (LNR), Lymph nodes with metastases (LNM), and factors of prognostic significance.

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INTRODUCTION

Colorectal cancer (CRC) is a very common gastrointestinal malignancy and is the major cause of death in the population worldwide. Colon cancers are common than the rectal and most of the CRC cases are treated by surgery.

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The most important prognostic factors regarding the colorectal cancers treatment are, the total number of lymph nodes examined, the number of lymph nodes with metastases (nodal stage N) and the lymph node ratio (LNR). LNR = the number of lymph nodes with metastases (positive LNs) to total number of lymph nodes examined. The histology of tumour, role of the surgeon and the pathologist, the patient age and comorbidities and mortalities due to surgical procedures are quite important regarding the prognosis of CRC.

TNM (tumour, lymph node and metastasis) system is used for staging and prognosis of malignancies. The minimum number of lymph nodes required to be examined for accurate staging is ≥ 12 .

The lymph node count in a surgical specimen positively correlates with; the age, gender, histology, location of tumour, size of the tumour, the differentiation of the tumour, the year of tumour diagnosis, the depth of

invasion of tumour, the experience and skill of surgeon and the interest and diligence of the pathologist.

Lymph nodes involvement by metastases predicts prognosis and is an important informative factor in deciding patient further treatment and also points towards tumour recurrence. These patients benefit from radio chemotherapy which decreases recurrence rate and increases disease free survival¹ and overall survival^{2,3}.

Goldstein et al⁴ suggested to retrieve and examined more and more lymph nodes during resection of a tumour. Many authors have reported improved survival in Dukes stages B and C with increased number of lymph nodes examined.

Berger et al⁵ noticed the ratio of metastatic lymph nodes to the total number of lymph nodes examined and concluded that lymph node ratio (LNR) is a significant prognostic factor for overall and disease free survival.

There are many factors which affect the number of lymph nodes (LNs) retrieval such as the type of surgical resection e.g. segmentectomy or hemicolectomy and also the number vary between patient to patient constitutionally⁶⁻⁸. The possibility of detecting positive lymph nodes pathologically increases with the number of lymph nodes examined⁹.

Age <65yrs and right sided tumour localization, the length of resected bowel segment and the spread of the tumour positively correlate with a high number of lymph nodes retrieved¹⁰.

Preoperative radio-chemotherapy decreases the number of lymph nodes retrieval⁸. Surgeon experience in colorectal surgery is an important factor in adequate lymph node recovery¹¹. Retrieval of lymph nodes and identification of positive lymph nodes have been shown to be significantly affected by pathologist lymph nodes examination⁹.

MATERIALS AND METHODS

The study was conducted on the data of 450 diagnosed cases of adenocarcinoma of colorectum who were admitted to the General Surgical Ward between January 2010 and Dec 2014. These patients underwent curative resection for colorectal cancer.

The data were collected from the clinical charts, computer record and pathological reports. Included in this study were males 290 (64.4%) and female 160 (35.5%). The mean age was 58.8±7.8yrs and the median age was 56(22-80) yrs. The mean age for female was 59.8yrs and for male was 57.5yrs.

Six experienced and skillful colorectal surgeons took part in the colorectal resection through an open approach. The surgical specimens were assessed by 2 interested and diligent pathologists. The resections were grouped as follow;

Rt hemicolectomies _____ 90.

Extended rt hemicolectomies _____ 15.

Transverse colectomies _____ 25

Lt hemicolectomies _____ 30.

Extended Lt hemicolectomies _____ 10.

Sigmoid resection _____ 85.

Anterior abdominal resection _____ 40.

with CME (complete mesocolic excision)

Abdomino perineal resection _____ 130.

with TME (total mesorectal excision)

Rectal extirpation _____ 25.

Preoperatively the patients were diagnosed by ultrasound abdomen and chest, CT scan abdomen and chest, X ray chest, sigmoid scopy and colonoscopy with biopsy and carcinoembryonic antigen (CEA) level.

Patients with more than one primary, patients with synchronous tumours, patients with distant metastases, patients with advanced irresectable tumours and patients who received neoadjuvant chemoradiation were excluded from the study.

The technique of total mesorectal excision (TME) or complete mesocolic excision (CME) was applied by sharp dissection in the developmental plane of the entire mesorectum or mesocolon with intact facial layers and ligation of the feeding vessels at their origin.

The length of the bowel excised was 10cms proximal and 10cms distal to the tumour growth in colon cancer and 5cms proximal and 2cms distal in the rectal carcinoma and the resected specimen removed en bloc with the mesorectum or mesocolon.

Follow up: From the record it was apparent that the patients had been followed for up to 5yrs. Patients had follow up check once every 3 months during the first year, once every 6 months during the next year and once in a year during the next 3years. During each follow up visit, patient physical examination, full blood count, CEA level, liver function tests (LFTs) and bone scan were repeated and surveillance colonoscopy and sigmoidoscopy done periodically. Survival data were collected by phone or interviews with patients or their relatives or from the record of our oncological department.

After a median follow up of 60months (55-65months); 370 patients were alive, 80 patient had died, of whom 70 patients from colorectal cancer (CRC). During each follow up check, patients were searched for any evidence of recurrence.

24.5% (n=90) patients postoperatively required radio chemotherapy within 4-8 weeks. 60 patients of rectal cancer received radiotherapy and 30 patients of colon cancer received chemotherapy.

Overall 19% patients (n=70) had cancer recurrence. Isolated liver metastases were found in 15 patients, isolated lung metastases in 8 patients and local recurrence was found in 30 patients.

Metastatic spread to liver commonly occurred from left sided colon cancer, while rectal cancers commonly metastasized to lungs and also these cancers had increase tendency for local recurrence.

RESULTS

Male patients of CRC were younger than females ($p < 0.05$). The frequency of CRC was higher in men (64.4%, $n = 290$) than the female (35.5%, $n = 160$). The mean number of lymph nodes retrieved was 15.8 ± 6.5 . More lymph nodes were found in patients with age < 65 yrs, the average was 17.5.

Table No.1: 5yr recurrence and survival rates in CRC patients.

Stage	Recurrence	5yr survival rates	
		Colon	Rectum
1	3.5%	75	70
11	10.9%	70	65
111a	25.4%	60	55
111b	39.6%	55	50

Table No.2: The Clinopathological data of 450 patients with CRC and the results of univariate analysis.

Variables	Number of pts	% of pts	5yr survival	P values
Gender				
Male	290	64.4	70	
Female	160	35.5	75	0.010
Age				
<65yrs	290	64.44	65	
>65yrs	160	35.55	60	0.05
Depth of invasion				
T ₁	45	10	65	
T ₂	115	27	60	
T ₃	210	49	55	
T ₄	54	12	50	0.001
Lymph nodes with mets				
N ₀	256	56.8	75	
N ₁	126	28	60	
N ₂	63	14	50	0.001
Lymph nodes examined				
<12	280	62.22	55	
>12	170	37.77	70	0.005
Tumour size				
>5cms	180	40	60	
<5cms	257	57	65	0.001
Low grade				
High grade	396	88	70	
High grade	54	12	55	0.001
Tumour type				
Adeno Ca	350	77.7	60	
Mucinous adeno Ca	70	15.5	55	
Invasive Ca	20	4.44	45	
Signet ring Ca	10	2.22	50	0.001

Regarding the location, more tumour were present in the colon, especially in the left colon (numbers given in the para as group resections). The mean number of lymph nodes examined were higher in the right colon (median=16) followed by left colon (the median number=14) and rectum (median=12). In 57% ($n = 257$) patients, the tumour showed a dimension of < 5 cms and in 40% ($n = 180$), the tumour dimension was > 5 cms with more serosal invasion.

Histologically the tumours were mostly adenocarcinoma 78% ($n = 350$), mucinous adenocarcinoma 15% ($n = 70$), followed by invasive adenocarcinoma 4.4% ($n = 20$) and the signet ring adenocarcinoma 2.2% ($n = 10$).

Regarding the spread of tumour, T₃ tumours were the most common 49% ($n = 210$), followed by T₂ 27% ($n = 115$). T₄ tumours were present in 12% ($n = 54$) and T₁ in only 10% ($n = 45$) cases.

Differentiated (low grade) tumours were more frequent 88% ($n = 396$) than the undifferentiated (high grade) tumours 12% ($n = 53$). In high grade tumours, the median number of lymph nodes retrieved was 17 while in low grade tumour it was 14.

Regarding the number of lymph nodes retrieved from a surgical specimen, it was < 12 in 62% of cases and > 12 lymph nodes per specimen were found in 38% of cases. In greater majority of cases 56.8% ($n = 256$), no lymph node with metastasis found, while in 28% ($n = 126$) 1-3 lymph nodes with metastases and in 14% ($n = 63$), > 4 lymph nodes with metastases found.

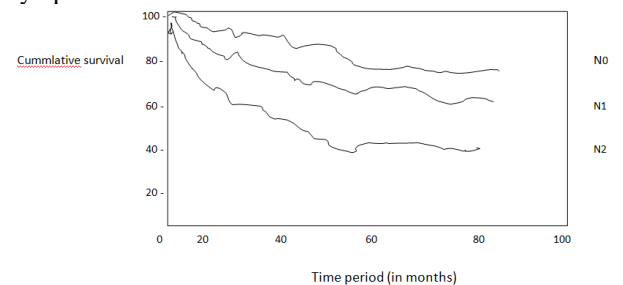
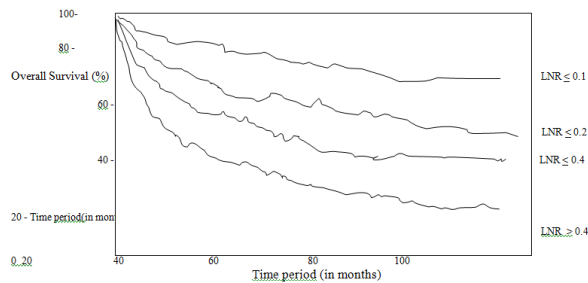


Figure No.1: Kaplan Meier survival curves according to the number of lymph nodes with mets.

There was a significant correlation between the number of lymph nodes removed and the lymph nodes with mets (Nstage) ($r = 0.138, p < 0.001$). While there was no significant positive correlation between the number of lymph nodes examined, the LNR and survival ($r = 0.026, p = 0.756$ and $r = 0.138, p = 0.065$) respectively.

In this study LNR was found to be significantly correlated with survival as the most significant prognostic factor [$p < 0.001, 95\% \text{ CI}; 3.14(1.45-5.65)$]. We noticed a correlation between the number of lymph nodes examined and the number of lymph nodes with mets (LNM or N stage) ($p = 0.005, r = 0.134$). The 189 patients (with N₁+N₂ diseases) were divided into 4 groups according to the LNR quartiles. i.e. LNR ≤ 0.1 $n = 60$, LNR ≤ 0.2 $n = 50$, LNR ≤ 0.4 $n = 45$ and LNR > 0.4 $n = 34$. The 5yr survival rates decreased as the LNR increased.



LNR<0.1 the 5yr survival was approximately 70%.
 LNR≤0.2 the 5yr survival was approximately 60%.
 LNR ≤0.4 the 5yr survival was approximately 55%.
 LNR>0.4 the 5yr survival was approximately 45%.

Figure No.2: Lymph nodes ratios and Kaplan Meier survival curves.

DISCUSSION

Total lymphadenectomy is a key factor in the curative surgery of CRC. The generally accepted recommendation demands at least 12 lymph nodes per surgical specimen¹². However the harvested lymph nodes number from a colorectal specimen is always highly variable and is incompletely understood¹³.

The surgeon and his skill and the pathologist and his devotion to his job are quite important regarding the number of lymph nodes harvest and the evaluation of lymph nodes respectively.

In this study we noticed that increased lymph node harvest was correlated with an increased number of lymph nodes with metastasis and which is according to the existing literature.

Levoyer et al¹⁴ concluded that the number of lymph nodes evaluated was a significant prognostic factor in both lymph nodes positive and negative patients of colorectal cancer.

Wright et al¹⁵ reported that 73% patients of CRC had <12 lymph nodes retrieved. In our study the number of patients with <12 lymph nodes retrieved were 62.22%.

Berger et al⁵ showed that decreased LNR was associated with increase survival. Decreased LNR shows either decreased positive lymph nodes or increase number of examined lymph nodes.

The technique of total mesorectal excision (TME) and complete mesocolic excision (CME) in colorectal surgery (the standardization of surgery) have led to improved survival and decreased recurrence¹⁶⁻¹⁷. Several authors have reported excellent outcome from TME or CME with good 5yr survival, low local recurrence and maximum lymph nodes yields.

CONCLUSION

In the management of CRC, the TNM staging system predicts the prognosis of the disease. The total number of lymph nodes and lymph nodes with metastases depend on the site of the tumour and extent of resection (surgeon skill), the handling of the resected specimen

(histopathologist role) and the pre and post operative radiochemotherapy protocols. The staging of a tumour depends upon the extent of spread through the bowel wall, the involvement of the number of lymph nodes in the drainage area, which dictates the management and predicts the survival and the recurrence rates of the disease.

The standardization of surgery (i.e. resection of a tumour in a clean sweep) and thorough retrieval and evaluation of the lymph nodes from the resected specimen (pathologist zeal and interest in searching out lymph nodes) which dictates an accurate staging and hence the prognosis of the disease.

Author's Contribution:

Concept & Design of Study: Gul Sher Khan
 Drafting: Abdul Ghafoor, Alam Zeb
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 Revisiting Critically: Gul Sher Khan, Abdul Ghafoor
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Conflict of Interest: The study has no conflict of interest to declare by any author.

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