

Incidence of apical lymph node (ALN) positivity in resectable colorectal cancer (CRC) and its prognostic significance on short term follow up at a tertiary care center in India

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Abstract: *Introduction:* Presence of lymph node metastases in colorectal cancer (CRC) is well recognized as one of the most important prognostic factors. Almost no data is available on Apical Lymph Node (ALN) positivity and its impact on survival and recurrence in India. Our study aims to bridge this gap. *Material and Methods:* 40 CRC patients deemed resectable on standard preoperative work up were included in the study. Apical lymph node and specimen were sent separately for histopathological examination and patients were divided into ALN positive (ALN+) and ALN negative (ALN-) groups. Patients were followed up for a period of 24 months. All patients were followed up with 3 monthly Carcinoembryonic Antigen (CEA) and Ultrasound abdomen, colonoscopy at 1 year and Computerized tomography (CT) abdomen at 1 year. *Results:* Of 40 patients 8 (20%) were ALN+. 30% (12/40) had recurrences of which 100% ALN+ cases(8/8) had recurrence but only 12.5% (4/32) of ALN- group had recurrence. In ALN+ group, all recurrences were distant metastasis whereas recurrences in ALN- group were 50% local and 50% distant metastasis. Mean recurrence free survival was 6months in ALN+ group while in ALN- group it was 10.5 months. 75% of ALN+ patients had elevated CEA level compared to 18.7% of ALN- group. Lymph Node ratio (LNR) was statistically higher in ALN+ group (60% versus 2.7% in ALN- group). *Conclusions:* ALN positivity was found to be 20% and correlated with higher preop CEA. ALN+ status was a significant risk factor for recurrence. ALN positivity is an indicator for higher recurrence rates and distant metastasis.

Keywords: Apical Lymph Node, Carcinoembryonic antigen, Circumferential Margin, Colorectal Cancer, Inferior mesenteric artery, Lymph Node Ratio.

Introduction

Colorectal cancer remains one of the most dynamic fields in oncology, both in the laboratory and in the clinic. The most easily identified risk factors include age greater than 50, a personal or family history of colorectal cancer or adenoma, and a personal history of long-standing inflammatory bowel disease [1]. Presence of lymph node (LN) metastases in colorectal cancer is well recognized as one of the most important prognostic factors for long-term outcome. Debate exists regarding the importance of increased LN harvests with a rationale to “improve” staging [2] as CEA is well established prognostic marker for CRC [3]. An important concept is that of the apical lymph node. It is broadly agreed that apical lymph nodes are the proximal most lymph nodes adjacent to origin of the feeding vessels [4]. Usually, it is the root of the inferior mesenteric artery (IMA) for left colon and rectum and the root of the ileocolic vessels for the caecum,

ascending colon and proximal two third of the transverse colon. However, the prognostic significance and impact on treatment is debated. Its positivity appears to be a strong independent, negative prognostic factor of poor survival in advanced colorectal cancers [5]. Some other investigators have doubted whether apical node harvesting leads to improved survival [6]. Therefore, the debate about apical lymph node and its prognostic significance is not yet over and needs further research. Thus, the objectives of our study is;

- (a) To determine the incidence of Apical Lymph Node positivity in resectable colorectal cancer.
- (b) To determine whether a positive apical lymph node in resectable colorectal malignancy has an effect on disease free survival, morbidity and mortality on short term follow up.
- (c) To formulate treatment protocol for apical node positive patients.

Material and Methods

Study Area: Cases for this study were taken from Department of Surgical Gastroenterology, Global Hospitals, Lakdi-ka-Pool, Hyderabad, India.

Study Population: Most patients in the study belonged to south India specially the states of Telangana, Andhra Pradesh and Orissa. All age groups were included. Patients with colorectal cancer of any stage were evaluated on outpatient or inpatient basis and included in the study as per inclusion and exclusion criteria

Sample Size and Sample Technique: 40 cases of Colorectal Resection for cancer were included in the study which was calculated as follows

$$N = Z^2(P(1-P)) / e^2$$

Where

"N" is the sample size,

- Z₂- is the abscissa of the normal curve that cuts off an area at the tails (1- equals the desired confidence level, e.g., 95%),
- e- is the desired level of precision,
- P- is estimated proportion of an attribute that is present in the population.

The value for Z is found in statistical tables which contain the area under the normal curve; e is level of precision. All these data were calculated using Open Epi online software (<http://www.openepi.com>) where standardized values were calculated automatically after estimating the incidence of colorectal malignancies in India [7]. This resulted in a sample size of approximately 40.

Data Collection Technique and Tools: A standard proforma was maintained and parameters and details filled in from the patient case sheet during their hospital stay. After patients were discharged, outpatient visits or inpatient admissions were recorded till June 7, 2015. Visits were scheduled every three months and results of laboratory tests and imaging was recorded in the study proforma. Cases were included only up to June 2014 so that a minimum follow up of 12 months is possible from the point of surgery. The complications, both immediate post op and long term, were recorded. Histopathological data including margins, number of positive lymph

nodes, apical lymph node positivity, total number of nodes examined, tumor dimensions, and perineural or lymphovascular invasion were noted as per proforma.

Data Analysis: The data was collected prospectively and data was analysed at the end of the study period. Incidence of Apical Lymph Node positivity in various stages of colorectal cancer was calculated using simple proportions. Apical node positive and negative patients shall form the two groups for comparison. For comparison of proportions, Pearson chi squared or Fisher Exact test was used, as appropriate. When comparing means in two independent samples, student t-test was used if data are of normal distribution. When data was skewed, a non-parametric test was used; means in two independent samples will be compared by Mann-Whitney test. Disease free survival, cancer specific survival and time to recurrence was calculated with Kaplan Meier Method. In all tests, a P value of < 0.05 was considered statistically significant.

Results

The mean age of the patients was 58.25 years (Range 33-78 years). There were 28 males (70%) and 12 females (30%). The average age in the ALN+ (apical lymph node positive) group was 52.75 years (Range 44-60 years) while in ALN-(apical lymph node negative) group was 59.37 years (Range 33-78 years). Out of the 8 patients who were ALN+, 2 were females (25%) and 6(75%) were males as compared to 5 females (15.6%) and 27 males (84.4%) in the ALN- group. Out of the 42 patients initially evaluated, 12 were located in the ascending colon (28.57%), 10 each in descending (23.8%) and sigmoid colon (23.8%). Rectum was the site in 8 patients (19.04%) and transverse colon was involved in 2 patients (4%).

Histopathological examination revealed adenocarcinoma in all patients (100%). Well differentiated adenocarcinoma was found in 2 out of 40(5%), moderately differentiated adenocarcinoma in 26 out of 40(65%), poorly differentiated adenocarcinoma in 2 out of 40(5%), Mucinous adenocarcinoma in 4 out of 40(10%) and carcinoma in situ in 6 out of 40(15%). Except one patient who presented

for the first time with colonic obstruction, all others had undergone pre-op colonoscopy and biopsy. This patient was later found to have poorly differentiated adenocarcinoma. All 4 patients with mucinous adenocarcinoma (100%) were ALN+. The other 4 patients who were ALN+ had moderately differentiated adenocarcinoma. As per the AJCC staging 6 patients of the ALN+ group (62.5%) were Stage III and 2 were stage II (37.5%). In the ALN- group, 4 were stage I (12.5%), 16 were stage II (50%) and 12 were stage III (37.5%). Stage IV patients were excluded from the study and 2 patients were excluded at time of surgery when they were found to have metastasis.

Lymph Nodes: Total number of positive lymph nodes was 110 out of a total yield of 632 nodes with a resultant lymph node ratio (LNR) of 0.174 or 17.4% positive nodes. The total number of lymph nodes positive in ALN+ group was 96 out of 177 total nodes which comprised almost 87.2% of all positive nodes and when broken down to ALN positive and ALN negative groups the LNR was 0.607 or 60.7% for the ALN positive group and 0.027 or 2.7% for the ALN negative group. This difference in LNR between ALN positive and ALN- groups was statistically significant ($p < 0.05$).

Follow up: All patients were followed up for a minimum of 12 months and a maximum of 24 months. CEA was monitored at 3,6,9 and 12 months and every 6 months thereafter, USG abdomen was done at 3 and 6 months and CECT scan and colonoscopy at 1 year. There was no mortality in both the ALN+ and ALN- groups.

Recurrence: Overall 12 patients had recurrence (30%) out of which 8 were ALN+ and 4 were ALN-. All 8 ALN+ had distant metastasis, defined as malignant ascites or multiple liver metastasis. Out of the 4 patients having recurrence in ALN- group 2 had local while 2 had distant metastasis (50% each). The 2 patients who had local recurrence had reoperation and local resection and are being followed up with no recurrence. This difference in ALN+ and ALN- groups was significantly higher when compared with Z test for proportions ($P < 0.05$). The median time to recurrence in ALN+ group was 5.6 months with 2 out of 8 (25%) having recurrence detected at 3 months 4 out of 8 (50%) at 6 months

and the remaining 2 (25%) at 1 year. The median time to recurrence in ALN- group was 10.5 months. The recurrence free survival is plotted on Kaplan Maeier curve. Median time to recurrence in ALN+ group was 5.6 months while it was 10.5 months in ALN- group. Using Log Rank test this was statistically significant for recurrence free survival ($P = 0.003$).

CEA: A CEA level of more than 5 ng/dl was considered as positive. Pre-operatively, 6 out of 8 (75%) ALN+ patients had elevated CEA with a mean of 24.49 ng/dl. In contrast, only 6 out of 32 (18.7%) had elevated CEA with a mean value of 2.59 ng/dl. This difference was statistically significant ($P = 0.02$). On follow up, Out of the 12 patients who had recurrence which include 8 of ALN+ and 4 of ALN- groups, 6 patients (50%) had elevated CEA at 6,9 and 12 months follow up. All these 6 patients were of the ALN+ group who had elevated CEA pre-operatively as well. 2 ALN+ (25%) patients did not have elevated CEA preoperatively and continued to have normal CEA in spite of having distant metastasis. No patients who had normal pre-operative CEA had elevated CEA postoperatively.

USG, CECT Scan and Colonoscopy: USG abdomen was repeated every 3 months while CECT abdomen and colonoscopy was done at the end of 1 year. In case the USG abdomen was suggestive of recurrence then CECT abdomen and X ray Chest was done to assess metastasis. 2 out of 8 ALN+ patients (25%) who had recurrence were picked up on USG abdomen at 3 months. Findings included ascites in both patients and CECT abdomen did not show any liver metastasis. Continued follow up at the end of 1 year showed multiple liver metastasis along with ascites despite continued palliative chemotherapy. 4 out of 8 patients (50%) were picked up at 6 months and 2 out of these had liver metastasis as well. All of these patients developed multiple liver metastasis by 1 year on CECT scan. 1 patient was diagnosed to have recurrence at 9 months and the other at 12 months, both with ascites and multiple liver metastasis. Colonoscopy at 1 year was normal in all patients in ALN+ group.

In the ALN- group, 4 out of 32(12.5%) had recurrence. 2 were picked up at 9 months (50%) and the other 2 at 12 months (50%). Patients in ALN- group who had recurrence at 9 months were picked up by USG scan which showed as cists with liver metastasis and the other 2 patients who were picked up at 12 months had local recurrence picked up by colonoscopy and CECT abdomen. All patients who had recurrence were diagnosed by 12 months. Patients who were further followed up for a maximum of 24 months did not have any recurrence.

Discussion

ALN generally speaking is the most proximal lymph node near the root of the vascular pedicle to the part of colon being resected [8-9]. In our study the ratio of males to females was 2:1 and reflected the general higher incidence of colorectal cancers in males as evident from incidence rates across Asia and indeed throughout the world. Here, though the mean age in ALN+ group was about 53 years (range 44-60 years), and in ALN- group was 60 years (range 33-86 years) this apparent difference in age did not reach statistical significance(P value 0.79).

In our study a laparoscopic approach was applied in all patients except when there was gross abdominal distention due to intestinal obstruction or for financial constraints. Out of the 6 patients who underwent open surgery, the mean hospital stay was 7 days with no immediate complications. For the laparoscopic group the mean hospital stay was 6.25 days and 2 out of 34(5.8%) required prolonged ICU care and stay. Due to the small numbers a meaningful comparison was not possible between the open and laparoscopic group, but the study conformed to the other major studies on laparoscopic colorectal resections [10-11]. There were no major complications, anastomotic leaks or peri-operative deaths. This could be in part attributed to the generally lower stage of the malignancy with majority being stage I and II tumors (55%) while 45% were stage III. Also, the lead surgeon was very experienced with specialized training in colorectal surgery. Surgeon's experience is an important reason for lower complications, mortality and morbidity [12].

The location of the tumor may have some impact on overall survival, with some studies showing

increased overall survival with left sided tumors [13-14]. In our study 75% of ALN+ patients had left sided lesions with all patients showing recurrence within 1 year. This is in contrast to the studies quoted earlier. This difference in part can be explained by mucinous histopathology in 50% of ALN+ patients. Also there were higher number of stage III tumors in the ALN+ group (75%). Whether the recurrence is due to unfavorable histopathology or the ALN status of the patient is debatable and will need large scale studies to elucidate.

Unplanned re-admissions included 2 patients who had local recurrence and were re-operated with uneventful post operative recovery. 2 other patients had sub-acute intestinal obstruction (SAIO) and both were re-operated. This gives an overall re-operation rate of 10% with half of these for recurrence and the half for SAIO. All other readmissions were for chemotherapy in a planned manner. Readmissions after colorectal surgery were analyzed in a meta-analysis which showed that bowel obstruction was the most common cause of unplanned readmission, accounting for 33.4% of all unplanned readmissions, followed by surgical site infection (15.7%) and intra abdominal abscess (12.6%) [15] 75% patients were from ALN- group and only 1 patient (25%) was from ALN+ group. All readmissions were within 1 year of index surgery, emphasizing the point that most complications occur within this period [16] and aggressive follow up must be done in the initial few months after surgery.

Circumferential margin (CM) is one of the most important predictors for recurrence and has an overall impact on survival [16]. Usually, involved CM is considered when distance from the edge of specimen to the tumor is less than 1mm [42]. For tumor location 6-15 mm above the anal verge, 2mm CM is considered sufficient, but for distal rectal cancers more than 1 mm is satisfactory [16]. In our study both ALN+ and ALN- groups had circumferential margins above 2mm for both right sided and left sided colon cancers and their mean difference in each group was similar. There were no patients of rectal cancer in ALN+ group and the CM for

the ALN- group was 1.74 mm. Therefore, all resections had good CM and it was not a confounding factor. Mean tumor size in our study in the ALN+ group was 5.5 cm while in ALN- group was 5.28 cm which was not statistically significant ($P > 0.05$). Perineural and lymphovascular invasion was present in 1/8 (12.5%) of ALN+ patients and in 2 of 32 (6.25%) in ALN- group and both had local recurrence. That such invasion is associated with increased risk of recurrence is well established [17]. In our study there was no statistical difference between ALN+ and ALN- groups as far as the perineural and lymphovascular invasion was considered. It is important to note that both patients in ALN- group with perineural and lymphovascular invasion had local recurrence while all ALN+ patients had distant metastasis which suggests that ALN positivity is a marker for early recurrence. Adequate proximal and distal margins are important for prevention of recurrence and disease clearance. All our resections were R0 thus eliminating any differences in the ALN+ and ALN- groups.

Prognosis of colorectal cancers have been linked to the location of the tumors in some studies. Generally right sided cancers have poor prognosis as compared to left sided cancers [18-20]. In our study, 6 out of 8 (75%) patients in ALN+ group were left sided cancers and all had recurrence. This is contrary to the studies mentioned. Most younger patients in India usually have rectal cancers [21]. No such predilection was noted in our study and all rectal cancers were found in patients above 50 years and all were ALN-. Hence, in our study poorer prognosis was found in left sided lesions (except rectum) as 75% of ALN+ group who had distant metastasis had left sided malignancy. These results should be read with caution because of small sample size and relatively late presentation of the disease in the Indian context where lack of application of screening methods in the general population leads to delayed diagnosis and more advanced stage of the disease at presentation.

Multiple studies have consistently demonstrated the importance and prognostic significance of the lymph node status in colorectal malignancies [22-25]. As per these studies, higher lymph node stage correlates negatively with survival. In our study, the ALN was dissected out in the operating

room after the specimen was taken out and sent for separate examination. This enabled both the surgeon and histopathologist to accurately stage the disease for the ALN status. Although LN status was positive in 18 out of 40 patients (45%), 8 out of these (44%) had ALN+ which meant a 20% incidence of Apical Lymph node positivity.

A higher lymph node ratio (LNR) has been associated with worse prognosis, earlier recurrence and shorter overall survival [26-28]. In our study, groups the LNR was 0.607 or 60.7% for the ALN positive group and 0.027 or 2.7% for the ALN negative group. This difference in LNR between ALN+ and ALN- groups was statistically significant ($p < 0.05$) suggesting that LNR is an important prognostic factor for recurrence and shorter disease free survival (DFS). Even though LNR seems to be a better indicator, the average number of LNs examined in ALN+ group was 19.75; in ALN- group was 15.4 suggesting adequacy of histopathological examination. Only 4 patients (10%) had fewer than 12 nodes examined out of which 2 had carcinoma in situ and underwent limited resection, yielding lesser nodes. 2 other patients were ALN- and had no recurrence up to maximum follow up. These data suggest that the total number of lymph nodes resected and examined are important for adequate staging but the prognosis depends on LNR and nodal stage rather than the total number of nodes examined.

Apical lymph node (ALN): ALN positivity is associated with overall poorer prognosis according to studies specifically focussing on ALN [3, 8, 26]. Overall, ALN positivity seems to have a negative impact on disease free survival (DFS) and overall survival (OS). The current AJCC nodal staging encompasses only the number of positive lymph nodes which suggests that a higher number of positive lymph node has a higher staging and hence poorer prognosis. A study by Peng et al [29] evaluated 510 patients with curative resection for node positive colorectal cancer and found that both the OS and DFS were significantly lower in the ALN+ group. They suggested that ALN metastasis is an important prognostic factor in node-positive rectal

cancer, Our study, though small, yielded similar results with 100% of ALN+ patients having recurrence within a year of follow up. Interestingly, all of these patients had distant metastasis suggesting that even though ALN does not count as a prognostic marker separately, metastasis in the ALN may be indicative of an already metastatic disease warranting a higher staging than just being classified as a “positive” lymph node in the current staging system. In a study by Ang et al [30], ALN positive patients did not have significantly different survival than patients who presented initially with distant metastasis. This suggests that patients who have ALN positive at initial analysis may already be having metastatic disease which is undetected.

Our study corroborates this assumption as all ALN+ patients had recurrence within a year and all were distant metastasis, indicative of the systemic nature of the disease in presence of a positive ALN. This raises a fundamental question as to whether ALN+ patients should be upstaged to distant metastasis. Large scale, long term studies are required to answer this question but our study is an important pointer for further investigation. As indicated in our study, the LNR in ALN+ group was significantly higher and almost half had aggressive tumors with mucinous type of adenocarcinoma with higher number of positive nodes. Whether the ALN metastasis specifically is an indicator of distant metastasis or a higher LNR, aggressive tumor type and multiple other poor prognostic factors indicate an already metastatic disease is a subject of further investigation.

Another important clinical correlate is the CEA level. 70% of patients with colorectal cancer will have an elevation in their CEA level at diagnosis, making it a useful marker for cure and surveillance of disease after surgery [31].

Our study showed a significantly higher pre-operative CEA level in ALN+ group ($P < 0.05$). The overall incidence of CEA above cutoff of 5ng/dl was 75% in ALN+ group and 18.7% in ALN- group giving an overall higher CEA of 22.5%. There are scarce studies in Indian populations on CEA cutoffs and the lower incidence of CEA secretors in our study in ALN- patients points towards good prognosis. Therefore, as demonstrated in our study, ALN+ patients had

significantly higher CEA levels which correlated with poor prognosis. Thus a combination of high CEA levels with separately examined positive ALN on histopathological examination may be used as a prognostic marker for recurrence, especially distant metastasis. As stated above further large scale studies will be needed before such a combination, if positive on both counts, can be labeled as metastatic disease (stage IV) rather than the stage II or III disease which is the current classification of resectable colorectal malignancy.

Follow up: Follow up in colorectal malignancies after resection is critical from two aspects. First is the early detection of recurrence which may be local or distant. The second important aspect of regular follow up is early detection of solitary liver metastasis without evidence of other disease. R0 resection of such an isolated liver metastasis confers some survival benefit although recurrence is common [32-33]. In our study we followed up patients at 3 monthly intervals with clinic visits, CEA levels, USG abdomen every 3rd month beginning at 6 months, CECT abdomen at 1 year and colonoscopy at 1 year after surgery. This approach was largely in accordance to the guidelines of the Indian Council for Medical Research (ICMR) sub-committee on colorectal cancer [43]. Such intensive follow up in the first 2 years after surgery is guided by the fact that most recurrences occur within the first two years and is defined as early recurrence [34].

We utilized this factor in our study which was limited by a maximum time of 24 months follow up. All recurrences which included 4 in ALN- group (12.5%) and 8 in ALN+ group (100%) occurred within 12 months. Except 2 patients in ALN- group who had local recurrence, all others were diagnosed by ultrasound of the abdomen which showed either liver metastasis, ascites or both. The patients with local recurrence were diagnosed at 12 months by colonoscopy and CECT scan. After the patients were suspected to have distant metastasis on ultrasound, CT chest and abdomen were immediately done to identify the extent of the metastasis. CT scan is 92.3% sensitive and 100% specific in staging

recurrent colorectal cancer in some studies, while others report a lower accuracy [36]. Positron emission tomography (PET) with ^{18}F -fluorodeoxyglucose (FDG) is a promising modality for the evaluation of recurrent CRC and Caglar et al reported sensitivity and specificity of 92% and 100% respectively [37]. Ultrasound (US) has a mean sensitivity of 69% in detecting liver metastasis which may be increased to 90% on contrast [38-39]. We included serial US in our study as it is a cheaper investigation, has no risk of radiation and was followed up by CECT at 12 months to pick up any missed early metastasis. Those who did not have recurrence up to the maximum follow up in the study are being continuously followed up by similar protocols.

Serial CEA levels were an integral part of the follow up and were repeated every 3 months. CEA is more frequently positive (greater than 5 ng/ml) in patients with advanced stage disease [31] and a similar results were seen in our study with the mean CEA in ALN+ group being significantly higher than that of the ALN- group. Out of the 4 ALN- group patients who had recurrence, no patient had serial rise in CEA levels as corroborative evidence and all were detected by either US, colonoscopy or CECT scan. CEA measurements can detect recurrent colorectal cancer with a sensitivity of approximately 80%, a specificity of approximately 70%, and can provide a lead time of approximately 5 months [44]. Amongst the 12 patients who had recurrence in our study, CEA was elevated in 50% preoperatively and serial CEA examinations rose were elevated in all of these at diagnosis of recurrence by US or CT. 2 other patients who had normal CEA preoperatively showed rise in CEA level before recurrence was detected (16.6%). Thus CEA levels not only indicates advanced stage of the disease but also helps in early detection of recurrence.

Recurrence: The most important factor in prevention of recurrence is an R0 resection [32]. In our study, local recurrence was found in 2 patients and both had rectal cancer(5%). Though R0 resection was achieved in both patients, both had perineural/lymphovascular invasion which is another risk factor for recurrence [34]. More than 50 % of CRC patients experience distant metastases during the course of malignancy and

the liver represents the predominant site of first metastatic relapse. Regarding international guidelines, there is interdisciplinary consensus that complete (R0) resection is the only curative option in the treatment of patients with colorectal cancer with liver metastasis [39]. Five-year overall survival rates up to 58 % have been reported by specialized centers [40], but primary liver resection is an option only in 20 % of patients[41]. Unfortunately, except 2 patients who had local recurrence in our study, 10 out of 12 patients had multiple liver metastasis, ascites or both leaving palliative chemotherapy as the only option. There was no mortality till the time of completion of study and patients are in regular follow up.

Several factors were important predictors of recurrence in our study. The fact that all resections were R0 and had adequate resection margins helped to evaluate other contributors to recurrence. Most important among these was the ALN+ status in which all 100% patients had recurrence and all were distant metastasis. High pre-operative CEA was found in 75% of ALN+ patients and 50% of all recurrences. Also all 4 patients with mucinous adenocarcinoma were ALN+ and had recurrence (100%). LNR was also higher in patients with recurrence as was the total number of positive nodes (mean of 8.0 nodes as compared to 0.42 nodes in patients with no recurrence). As mentioned earlier, whether ALN+ status along with high pre-operative CEA should be considered as metastatic disease needs further evaluation and large scale studies. This study attempts to bridge this gap and though small in scale, indicates the importance of ALN+ status as a marker for probable metastatic disease.

Shortcomings of the study: First is the small sample size of 42 patients out of which 20% or 8 patients were positive for ALN and 2 were excluded. Although characteristics of both these group showed significant differences, higher powered studies would better elucidate these apparent differences.

Secondly, the study was limited by short term follow up. Although most recurrences occur by 24 months, this study duration is still not

long enough to account for all recurrences, about 90% of which seem to occur by 50 months in rectal cancer and 28 months in colon cancer [35]. We agree that a longer follow up would elucidate further differences between the two groups.

Lastly, the incidence of ALN positivity was found to be 20% in our study which is much higher than other studies in the literature [3, 30]. This may be in part due to late presentation and lack of screening programs in our country. However, definite conclusions may not be drawn as screening data is scarce and the incidence of colorectal cancer in India is much lower than other countries [9].

Conclusions

Though small in scale and short on follow up, certain conclusions can be drawn from this study:

1. The incidence of ALN positivity in resectable colorectal malignancy is 20% in south India.
2. Pre operative CEA is significantly elevated in patients who were found to have ALN+ on histopathology as compared to ALN- patients.
3. ALN positivity is a significant risk factor for recurrence, especially distant metastasis, as all patients with ALN+ nodes developed distant metastasis which was significantly higher than ALN- group
4. Mucinous adenocarcinoma on histopathology is a significant risk factor for recurrence. All patients with Mucinous adenocarcinoma had ALN+ and all had distant metastasis within 1 year
5. ALN + patients were associated with mucinous histopathology, higher N stage, higher LNR and left sided malignancies(except rectum).

Recommendations

1. Colorectal Malignancies have the lowest incidence in amongst all Asian countries but

the patients tend to present late as evidenced with 20% incidence of Apical Lymph Node positivity in our study. Hence it is advisable that large scale screening programs should be employed as in the western countries for early detection of colorectal malignancies

2. Apical Lymph Node is an important marker for poor prognosis and we recommend that it should be separately dissected from the operative specimen and examined separately on histopathological examination to aid in prognostication
3. Serum CEA (Carcino-embryonic Antigen) is a well established marker for colorectal malignancies, especially for follow up. However we recommend that higher CEA values should be taken as a prognostic marker for advanced malignancy, especially if Apical Lymph Node is positive post operatively.
4. The current American Joint Committee on cancer (AJCC) classification does not include the CEA as a marker for poor prognosis. Also the nodal stage is linked to number of positive lymph nodes rather than the level of lymph nodes. We recommend that Apical Lymph Node with a combination of high pre-operative CEA should be further investigated in large scale studies and included in the classification scheme as it indicates worse prognosis even in lower staged disease as per current classification.
5. Laparoscopic approach should be adopted in most cases of resectable colorectal malignancies, unless gross bowel distention is present or financial considerations are there. For widespread application of laparoscopic approach, specific laparoscopic colorectal training programs should be initiated to extend the well known benefits of minimally invasive approach to the general population.

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