

Co-Relation of Clinico-Pathological Features With Prognosis (Outcome) in Patients With Colorectal Cancer.

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ABSTRACT:

Present study is done with an aim to co-relate the clinico-pathological features with prognosis (outcome) in patients having colorectal cancer.

The colorectal cancers usually occur in patients >50 years of age (independent predictor of poor prognosis) but can occur in younger individuals as well. There is a male predominance in occurrence with male: female ratio of about 3:2. The majority of patients lie between the age group of 41-70 years.

Rectal bleed, change in bowel habits, chronic abdominal pain and generalized weakness are the common forms of presentation. Rectum is the most common site of presentation and majority of them present with proliferative growth on colonoscopy and CECT abdomen. The most common reported site of obstruction is the sigmoid colon.

Despite having a more advanced cancer (aggressive form), the younger patients do not have a poor prognosis compared to the older ones. The right-sided and left-sided colon cancers have different disease characteristics due to differences in their embryological origin.

In terms of pathological characteristics, the right-sided colon cancers have more mucinous type cancer, more poorly differentiated tumors and more advanced TNM stage, more distant metastasis, higher incidence of peritoneal seeding and thereby peritoneal carcinomatosis. Patients with left-sided colon cancers have higher incidence of hepatic metastasis, pulmonary metastasis and better survival outcomes.

Early detection strategies such as screening at a younger age may improve the survival of the younger patients. On comparing the emergency with elective surgeries done for colorectal cancers, the emergency colo-rectal surgeries were associated with a poorer outcome, higher recurrence and mortality rates.

Keywords: Colorectal cancers, Co-relation, Clinico-pathological features, Prognosis.

Study Design: Meta-analysis.

1. INTRODUCTION:-

Colorectal carcinoma (CRC) is one of the most frequent malignancies in the world¹. The colorectal cancer is the third most common cancer in men (746,000 cases, 10% of the total) and the second most common in women (614,000 cases, 9.2% of the total) worldwide². Its incidence rates are rising rapidly in India which vary according to age, gender and race³. Although colorectal carcinoma is thought to be a malignancy occurring primarily in patients older than 50 years of age; likelihood the disease is an unusual finding in patients under 40 years age⁴. It has been estimated that about 2-3% of colorectal cancers occur in

patients less than 40 years of age⁵. However, current studies have suggested an increased incidence of colorectal cancers in younger age group in India as well as worldwide^{6,7}. Colorectal cancer is a malignant neoplasm arising from the lining of the mucosa of colon and rectum. It develops by a multistep process that is influenced by hereditary or genetic and environmental or acquired factors or inflammatory conditions of digestive tract. An individual with a history of either adenomatous polyps or inflammatory bowel disease has an increased risk of developing colorectal cancer compared to an individual with no history of either^{8,9}. The treatment, prognosis and survival rate depends on the stage of disease at diagnosis. Screening can prevent cancer from occurring as it can detect adenomatous polyps (pre-neoplastic lesions) that can be successfully removed¹⁰. According to Moertel's definition in terms of chronicity the colorectal cancers can be single cancer, synchronous cancer (more than one primary colorectal cancer detected in a single patient simultaneously or within 6 months of initial diagnosis), metachronous cancer (primary colorectal tumor developing after 6 months of previous colorectal surgery for colorectal carcinoma)¹¹. Some studies have demonstrated that young CRC patients presented poor pathological features and advanced stage compared with older patients¹². O'Connell et al⁵ reported that young CRC patients with early stage had better overall 5-year survival rates than older patients. Around 15-30% of CRC's present as a surgical emergency, with the most common cause being obstruction (78%), perforation (10%), or bleeding (4%)^{13,14}. Rectal cancers seldom present as an emergency (5.9%), while this is much more likely with colon cancers (21.7%)¹⁴. The left colon and the sigmoid colon are the most common sites of tumor obstruction, but the risk of obstruction is highest at splenic flexure^{15,16}. The sigmoid and caecum are the most common sites for perforation¹⁷. Perforation can occur either at the site of tumor or proximal to it, and is a serious condition which apart from risk of tumor cells seeding, can cause generalized peritonitis or abscess formation¹⁸. The advanced stages and poor histologic features of CRC are more likely to be observed in younger patients than in the older ones, which require more aggressive treatments^{19,20}. The prognosis of the younger CRC patients is an important issue due to the impact of disease and its treatment strategies on their fertility, career, life expectancy and emotional behaviour²¹. The current treatment options of colorectal cancer consists of surgery for early-stage disease and the combination of surgery and adjuvant therapy for advanced stage disease²². Colonoscopy is an invasive procedure for diseases of the lower gastrointestinal tract²³. It is utilized for both diagnostic and therapeutic purposes²³. Direct visualization makes it an investigation of choice for various pathologies of colon²³. Polypectomy during colonoscopy has been shown to decrease the incidence of CRC and associated mortality²³. Patients who are not good candidates for colonoscopy can be evaluated using CECT (Contrast Enhanced computed Tomography) abdomen and CT colonography²³.

In embryogenesis, the right colon which comprises of caecum and proximal two-thirds of transverse colon, arises from the midgut²⁴. Meanwhile, the left colon, which comprises of distal one-third of transverse colon to the rectum, arises from the hindgut²⁴. The proximal colon cancers are more genetically stable form of the disease, while distal colon cancer has greater genetic instability²⁴. Right sided colon cancer tends to initially present as anaemia and weight loss, while changes in the bowel movement and hematochezia are the initial symptoms in left sided colon cancer²⁵. Patient with right-sided colon cancer tend to be women, elderly, have more advanced tumor staging and have a mucinous type²⁶. The prognosis of left-sided colon cancer has improved since 1980, but that of right-sided colon cancer remains poor²⁷. The risk of distant metastasis, particularly peritoneal and nodal metastasis is higher in right-sided colon cancer than in left-sided colon cancer²⁸.

2. MATERIAL AND METHODS:-

Various studies conducted on patients with colorectal cancer including the clinical entities (age, gender, associated GI problems and comorbid conditions) and histopathological (histologic types) entities, tumor location, cancer numbers, size of tumor, number of lymph nodes involved along with prognosis were included in this study and their interpretations were studied and analyzed.

3. RESULTS:-

A total of 7 different studies were included and the clinical features along with histologic types of colorectal cancer were correlated along with the prognosis, location, age, differentiation, treatment modality, post surgical complications and hospital stay. These studies and their interpretations are as follows:-

S.NO.	STUDY BY/DURATION/ PLACE/ SAMPLE SIZE/ TYPE OF STUDY	RESULTS	INTERPRETATION
1.	Tapas Patra et al.(Jan.2012-July2016), Kolkata,India ²⁹ . On 420 patients. Retrospective study.	46.2% of the total cancer lesions occurred in rectum. Mucinous adenocarcinoma cases were 23.6% and mostly in younger age group (65.7%). Patients of synchronous liver metastasis had 18.8% and with DM type2 had 16.7% chances of developing colorectal cancer.	Rectum is the most common site for occurrence of colorectal cancer. Mucinous adenocarcinoma most commonly occurred in younger patients. The highest frequency of developing colorectal cancer was in patients with synchronous liver metastasis followed by Type2 diabetes patients.
2.	Rui Wang et al. (1988- 2011), USA ³⁰ . On 279,623 patients. Cohort study.	Patients were divided into 3 groups of 20-40years, 41-50years and more than 50 years. The older age group had a hazard ratio of 1.545. The tumors located on the right colon were 29.8% in 20-40 years age group and 28.2% in 41-50 years age group.	The older age was an independent predictor of poor prognosis. Tumors located in the right colon were seen less frequently in young patients. Young CRC patients had more tumors located in rectum, fewer cases with multiple tumors, later stage, more mucinous carcinoma and signet- ring cell carcinoma, more poorly differentiated tumors and more lymph nodes (>12)

			examined, they had later stage presentation, more aggressive pathological features but better prognosis.
3.	Sam Ghazi et al. (2004-2006); Stockholm, Sweden ³¹ . On 976 patients (8 hospitals). Univariate/ Multivariate analysis.	Patients having CRC's and undergoing emergency surgery had multiple tumors, high number of tumor infiltrating lymphocytes, signet ring cell mucinous carcinoma, desmoplastic stromal reaction, vascular invasion, perineural invasion and an infiltrating tumor margin.	Colorectal cancers undergoing emergency surgery generally show a more aggressive histopathologic profile and a more advanced stage than those undergoing elective surgery.
4.	Robabeh Ghodssi-Ghassemabadi et al. (2008-2013); Tehran, Iran ³² . On 396 patients. Retrospective study.	Patients <50years (younger group) were 39.4% and patients >50years (older group) were 60.6% of total. Various symptoms seen in patients were rectal bleed (47.4% in younger group and 46.7% in older group), change in bowel habits, abdominal pain, melena, obstruction. The younger patients had a significantly poor tumor grade than the older ones. In younger patients incidence was 66.7% and in older ones it was 55%. Patients with pre operative CEA >5 had a death rate of 41%.	Patients with CRC were more in older age group (>50 years). Rectal bleeding was the most prevalent symptom in both age groups followed by change in bowel habits. Younger patients had poor tumor grade while the older patients had more prevalent co-morbidities. Elevated pre operative CEA levels increased the hazard of death.
5.	Phillipo L Chalya et al. (July 2006-June 2011) ; CUHAS-Bugando, Tanzania ³³ . On 332 patients. Retrospective study.	The duration of symptoms at presentation ranged from 3 weeks to 7 years. There were 60.8% left sided (distal colon), 23.5% right sided (proximal) and 15.7% rectal tumors. The	The median duration of symptoms was 22 months. Left sided (distal colon) tumors were more common. Recto- sigmoid region was the most frequent site for colorectal cancer.

		<p>colorectal cancer at recto- sigmoid region were 54.8%, caecum 12%, ascending colon 7.5%, descending colon 6.0% and transverse colon 3.9% . Macroscopically, right sided tumors were fungating while left sided were flat and infiltrating. Mucinous and signet ring carcinoma accounted for 11.6% and 4.6% patients. Mucinous adenocarcinomas had a frequency of 9.8% in right side colon and 1.8% in left side colon. Left hemicolectomy was performed in 58.6% of the cases. About 16.8% patients received adjuvant therapy. Post operative complications were recorded in 26.2% cases like surgical site infection (41.9%), perianal wound breakdown(12.8%), intra- abdominal abscess/ peritonitis(9.3%), anastamotic breakdown(5.8%), chest infections (5.8%), anemia(4.7%), septicemia(4.7%), renal failure(2.3%) and deep vein thrombosis(1.2%). The overall hospital stay ranged from 4-72 days.</p>	<p>Macroscopically, right sided tumors were fungating, nodular with surface ulcerations while left sided tumors were flat, infiltrating or constricting. Microscopically, adenocarcinoma was the most common histologic pattern, the majority of which were moderately differentiated. Mucinous carcinomas and signet ring carcinomas were more common in patients under 40 years of age along with a poor prognosis. The mucinous adenocarcinomas were more frequent in right side of colon. Left sided hemicolectomy was the most frequent surgical intervention done. The surgical site infection was the most common post operative complication. The median duration of overall hospital stay was 12 days.</p>
6.	<p>Subash Bhattarai et al. (Jan. 2018-June 2020); MCMS, Nepal³⁴. On 52 patients. Descriptive cross sectional study.</p>	<p>The patients presented with complaints of change in bowel habits(92.3%) and abdominal pain(84.6%) mostly. Various clinical signs seen were</p>	<p>Change in bowel habits and abdominal pain were the most common symptoms while pallor was the most common sign. Rectal carcinoma was the commonest</p>

		<p>pallor(75%), abdominal tenderness(69.2%), palpable abdominal mass(25%).CECT abdomen revealed findings suggestive or suspicious of colorectal malignancies in 75% patients. Rectal carcinoma was seen in 35% cases. 65.4% of colonic carcinoma were left sided. 51.9% of adenocarcinomas were moderately differentiated.</p>	<p>colorectal carcinoma. Almost 2/3rd of colonic carcinomas were left sided. Most of the adenocarcinomas were moderately differentiated.</p>
7.	<p>Yu Lun Hsu, Chun Chi Lin et al.(2000-2010);VGH, Taipei, Taiwan³⁵. On 1503 patients. Comparative study.</p>	<p>A total of 66% patients were male and 34% were female. In right-sided colon cancer 42% were females while in left- sided colon cancer 31.7% were females. The left- sided colon cancers had 91.2% cases of adenocarcinoma type while right- sided colon cancers had 7.4% of mucinous type (mucin>50%). Patients with right- sided colon cancer had 11.5% of poorly differentiated tumors. In cases of tumor recurrence, the risk for peritoneal tumor seeding was 12.8% in right- sided colon cancer and 5.7% in left-sided colon cancer. Survival outcome in left- sided colon cancer was better. Patients with microsatellite instability were known to have better survival.</p>	<p>CRC showed to have a male preponderance. The proportion of females was higher in right- sided colon cancer. The left- sided colon cancers were predominantly adenocarcinoma while the right- sided colon cancers were mucinous type. Patients with right- sided colon cancer had more advanced TNM stage and more poorly differentiated tumors. Mutations were more abundant in right-sided colon cancers than in left- sided. In cases of tumor recurrence, the risk for peritoneal tumor seeding was higher in right- sided colon cancer group. Survival outcome in left- sided colon cancer was better than right- sided. Patients with microsatellite instability were known to have better survival.</p>

4. DISCUSSION:-

The majority of patients having colorectal carcinoma (CRC) lie between the age group of 41-70 years. However, it is not uncommon in younger age. There is a male predominance in occurrence with male:female ratio of about 3:2

Tumor stage and differentiation are important negative factors that affect the patients survival, as patients with stage 4 have poor prognosis than stage 1. A poorly differentiated tumor is associated with decreased survival. The pre operative CEA is a good prognostic of survival, especially among older patients. Higher pre operative CEA levels leads to poor prognosis in older individuals, while there is no association between pre operative CEA and prognosis in young individuals. The proportion of patients with stage 4 are higher in younger age group. Poorly differentiated tumors and rectal tumors are significantly more common in younger patients compared to the older. Although, poor grade patients are more likely to have a poor prognosis, but probably the younger patients may undergo a more aggressive treatment which might lead to a good survival rate. The rectum is the most common tumor site in younger group and the cancer stage is the predominant factor affecting the survival. The late presentation of patients with CRC in developing countries may be attributed to lack of awareness of the disease, low standard of education, lack of accessibility to health care facilities and lack of screening programmes. Detecting colorectal cancer at an early stage contributes to improved chances for successful treatment and thus for survival. Rectal bleeding is the commonest symptom in patients of colorectal cancer followed by change in bowel habits and significant weight loss in last 6 months. Higher rate of rectal bleed is attributed to large number of patients with left- sided tumors particularly the recto- sigmoid and ano-rectal tumors. Macroscopically, tumors on the right side (ascending colon and caecum) tend to be exopytic; that is the tumor grows outwards from a location in bowel wall. This very rarely causes obstruction of feces and presents with symptoms such as anaemia. Left sided tumors tend to be circumferential and can obstruct the bowel much like a napkin ring. Microscopically, the histologic types are adenocarcinomas (most common) arising from epithelial lining of colorectum, mucinous, signet ring cell, non- hodgkin's lymphoma, malignant gastrointestinal stromal tumors, leiomyosarcoma and squamous cell carcinoma. Patients <40 years of age tend to have poor prognostic tumors such as mucinous and signet-ring carcinoma. Mucinous carcinomas have been associated with poor prognosis, poor response to chemotherapy, tend to be located in proximal colon and associated with microsatellite instability. Treatment modalities of colorectal cancer include surgery combined with chemotherapy and radiotherapy given either as neo or adjuvant therapy. Surgical therapy continues to be the primary treatment option for CRC patients and colon/ rectal resection has been the standard procedure for cancer primarily localized to colon/ rectum. Complete resection of colorectal cancer with resection of adjacent lymph node is the only chance of cure in early- stage cancer. Radiation therapy has been shown to improve local control rates in locally advanced colorectal cancers when applied preoperatively or postoperatively. The higher complication rates are attributed to late presentation and delayed definitive treatment. The median duration of hospital stay is higher due to higher rates of post operative complications which require additional operations/care and subsequently prolonged hospital stay. The right- sided and left sided colon cancers have different disease characteristics due to differences in their embryological origin. Patients with right- sided colon cancer are older than those with left- sided colon cancer. In terms of pathological characteristics, the right-sided colon cancer group have more mucinous type cancer, more poorly differentiated tumors and more advanced TNM stage, more distant metastasis, higher incidence of peritoneal seeding and thereby peritoneal carcinomatosis. Patients with left- sided colon

cancer have higher incidence of hepatic metastasis, pulmonary metastasis and better survival outcomes.

5. CONCLUSION:-

- ❖ The colorectal cancers usually occur in patients >50 years of age (independent predictor of poor prognosis) but can occur in younger individuals as well.
- ❖ There is a male predominance in occurrence with male:female ratio of about 3:2. The majority of patients lie between the age group of 41-70 years.
- ❖ Rectal bleed, change in bowel habits, chronic abdominal pain and generalized weakness are the common forms of presentation.
- ❖ Rectum is the most common site of presentation and majority of them present with proliferative growth on colonoscopy and CECT abdomen.
- ❖ The most common reported site of obstruction is the sigmoid colon.
- ❖ Patients <40 years of age tend to have poor prognostic tumors such as mucinous and signet- ring carcinoma.
- ❖ Despite having a more advanced cancer (aggressive form), the younger patients do not have a poor prognosis compared to the older ones.
- ❖ Mucinous carcinomas have been associated with poor prognosis, poor response to chemotherapy, tend to be located in proximal colon and associated with microsatellite instability.
- ❖ The right- sided and left sided colon cancers have different disease characteristics due to differences in their embryological origin.
- ❖ The right- sided colon cancers have a higher risk for peritoneal metastasis and poor outcomes. In terms of molecular characteristics, The right- sided colon cancers have more gene mutations in BRAF, KRAS, SMAD4, TGF-B, PIK3CA and MSI- High. Overall survival is better in left- sided colon cancers. Meanwhile, in right- sided colon cancers, those with MSI have significantly better survival.
- ❖ In terms of pathological characteristics, the right- sided colon cancers have more mucinous type cancer, more poorly differentiated tumors and more advanced TNM stage, more distant metastasis, higher incidence of peritoneal seeding and thereby peritoneal carcinomatosis.
- ❖ Patients with left- sided colon cancers have higher incidence of hepatic metastasis, pulmonary metastasis and better survival outcomes.
- ❖ Early detection strategies such as screening at a younger age may improve the survival of the younger patients.
- ❖ On comparing the emergency with elective surgeries done for colorectal cancers, the emergency colo-rectal surgeries were associated with a poorer outcome, higher recurrence and mortality rates.

6. REFERENCES:-

- [1] Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008; GLOBOCAN 2008. *Int J Cancer*. 2010; 127:2893-2917.
- [2] GLOBOCAN. Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012;2012. <http://globocan.iarc.fr>.
- [3] Mohandas KM, Desai DC. Epidemiology of digestive tract cancers in India. V. Large and small bowel. *Indian J Gastroenterol*. 1999;18:118-121.
- [4] Walton WW, Hagihara PG, Griffen WO. Colorectal adenocarcinoma in patients less than 40 years old. *Dis. Colon Rectum*. 1975;19:529-534.
- [5] O'Connell JB, Maggard MAL, Livingston EH, Yo CK. Colorectal cancer in the young. *Am J Surg*. 2004;187:343-348.

- [6] Pal M. Proportionate increase in incidence of colorectal cancer at an age below 40years: An observation. *J. Cancer Res Ther.* 2006;2:97-99.
- [7] KalwarA, Nirban RK, KapoorA, Narayan S, Kumar N, Maharia S. Five year survival analysis of colon cancer: A retrospective study.*J. Gastroenterol Hepatol Res.* 2013;2(12):929-933.
- [8] Haskell CM. *Cancer treatment.* Philadelphia: W.B. Saunders Company; 2001: 704-705.
- [9] Hagggar FA, Boushey RP. Colorectal cancer epidemiology: Incidence, mortality, survival and risk factors. *Clin Colon Rectal Surg.* 2009;22(4):191-197.
- [10] Rex DK, Eid E. Considerations regarding the present and future roles of colonoscopy in colorectal cancer prevention. *Clin. Gastroenterol. Hepatol.*2008;6(5):506-514.
- [11] Moertel CG. Multiple primary malignant neoplasms: Historical Perspectives. *Cancer.* 1977;40(Suppl 4):1786-1792 [PubMed] [Google Scholar].
- [12] Gallagher EG, ZeiglerMG. Rectal carcinoma in patients in the second and third decades of life. *Am J Surg.*1972;124:655-659. O; Connell JB, Maggard MA, Liu JH et al. Are survival rates different for young and older patients with rectal cancer? *Dis Colon Rectum.* 2004;47: 2064-2069.
- [13] Scott NA, Jeacock J, Kingston RD: Risk factors in patients presenting as an emergency with colorectal cancer. *Br J Surg.* 1995,82(3):321-323.
- [14] Wong SK, Jalaludin BB, Morgan MJ, Berthelsen AS, Morgan A, Gatenby AH, Fulham SB: Tumor pathology and long term survival in emergency colorectal cancer. *Dis Colon Rectum* 2008, 51(2):223-230.
- [15] Carraro PG, Segala M, Cesana BM, Tiberio G: Obstructing colonic cancer: Failure and survival patterns over a ten- yearfollow- up after one- stage curative surgery. *Dis Colon Rectum* 2001, 44(2):243-250.
- [16] Lee YM, Law WL, Chu KW, Poon RT: Emergency surgery for obstructing colorectal cancers: A comparison between right- sided and left- sided lesions. *J Am Coll Surg* 2001, 192(6): 719-725.
- [17] Bass G, Fleming C, Conneely J, Martin Z, Mealy K: Emergency first presentation of colorectal cancer predicts significantly poorer outcomes: A review of 356 consecutive Irish patients. *Dis Colon Rectum* 2009, 52(4):678-684.
- [18] Sam Ghazi, Elisabeth Berg,Annika Lindblom, Ulrik Lindforss. Clinicopathological analysis of colorectal cancer: A comparison between emergency and elective surgical cases.*World J. Of Surg. Onco.*2013,11:133;1-11.
- [19] Silla IO, Rueda D, Rodriguez Y, Garcia JL, dela Cruz VF, Perea J. Early onset colorectal cancer: A separate subset of colorectal cancer. *World J Gastroenterol: WJG* 2014;20(46):17288.
- [20] Zhao L, Bao F, Yan J, Liu H, Li T, Chen H et al. Poor prognosis of young patients with colorectal cancer: A retrospective study. *Int. J Color Dis.*2017;32(8):1147-56.
- [21] Campos FG. Colorectal cancer in young adults : A difficult challenge. *World J Gastroenterol.* 2017;23(28):5041.
- [22] Cunningham D, Atkin W, Lenz HJ, Lynch HT, Minsky B, Nordlinger B, Starling N: Colorectal cancer. *Lancet* 2010, 375:1030-1047.
- [23] Winawer SW, Fletcher RH, Mille L, Godlee F, Stolar MH, Mulrow CD et al. AGA guidelines: Colorectal cancer screening: Clinical guidelines and rationale, *Gastroentology.* 1997;112(2):594-642. DOI:10.1053/gast.1997.v112.agast970594 PMID:9024315.
- [24] Bufill JA. Colorectal cancer: Evidence for distinct genetic categories based on proximal or distal tumor location. *Ann Intern Med* 1990;113(10):779-788.

- [25] Lee GH, Malietzis G, Askari A et al. Is right- sided colon cancer different from left- sided colon cancer?- A systematic review. *Eur.J. Surg. Oncol.*2015;41(3):300-308.
- [26] Sideris M, Adams K, Moorhead J et al. BRAF V600E mutation in colorectal cancer is associated with right- sided tumors and iron deficiency anaemia. *Anticancer Res* 2015;35(4):2345-2350.
- [27] Mik M, Berut M, Dziki L et al. Right and left- sided colon cancer- Clinical and pathological differences of the disease entity in one organ. *Arch Med Sci* 2017;13(1):157-162.
- [28] Yang J, Du XL, Li ST et al. Characteristics of differently located located colorectal cancers support proximal and distal classification: A population based study of 57,847 patients. *PLoS One* 2016;11(12):e0167540.
- [29] Mik M, Berut M, Dziki L et al. Right and left- sided colon cancer- Clinical and pathological differences of the disease entity in one organ. *Arch Med Sci* 2017;13(1):157-162.
- [30] Gervaz P, Usel M, Rapiti E et al. Right colon cancer: Left behind. *Eur J Surg Oncol* 2016;42(9):1343-1349.
- [31] Lee S, Cho NY, Choi M et al. Clinicopathological features of CpG island methylator phenotype- positive colorectal cancer and its adverse prognosis in relation to KRAS/BRAF mutation. *Pathol Int* 2008;58(2):104-113.
- [32] Murcia O, Juarez M, Hernandez- Illan E et al. Serrated colorectal cancer: Molecular classification, prognosis and response to chemotherapy. *World J Gastroenterol* 2016;22(13):3516-3530.
- [33] 29. Tapas Patra, Shyamsundat Mandal, Neyaz Alam, N. Murmu. *Clinical Epidemiology and Global Health.* 2018 (6):39-43.
- [34] 30. Rui Wang, Mo-Jin Wang, Jie Ping. Clinicopathological features and survival outcomes of colorectal cancer in young versus elderly. *Md. Journal* 2015 Vol.94,No. 35:1-8.
- [35] 31. Sam Ghazi, Elisabeth Berg, Annika Lindblom, Ulrik Lindfors. Clinicopathological analysis of colorectal cancer: A comparison between emergency and elective surgical cases. *World Journ. Of Surg. Onco.*2013,11:133;1-11.
- [36] 32. Robabeh Ghodssi Ghassemabadi, Ebrahim Hajizadeh, Shaghayegh Kamian, Mahmood Mahmoudi. Clinicopathological features and survival of colorectal cancer patients younger than 50 years: A retrospective comparative study. *Jour. Of Egyptian National Cancer Institute.* 2019;31:6.
- [37] 33. Philipo L Chalya, Mabula D Mchembe, Joseph B Mabula, Peter F Rambau, Hyasinta Jaka, Mheta Koy, Eliasa Mkongo, Nestory Masalu. Clinicopathological patterns and challenges of management of colorectal cancer in a resource- limited setting: A Tanzanian experience. *WJSO*;2013,11:88.
- [38] 34. Subash Bhattarai, Om Bahadur Karki, Merina Gyawali, Sudeep Regmi. Clinicopathological profile of colorectal carcinoma in a tertiary care teaching hospital in Pokhara, Nepal. *Jour. Of Gandaki Medical College- Nepal.*2021;14(2):14-8. DOI:10.3126/jgmcn.v14i1.30966.
- [39] 35. Yu Lun Hsu, Chun Chi Lin, Jeng Kai Jiang, Hung Hsin Lin, Yuan Tzu Lan, Huann Sheng Wang, Shung Haur Yang, Wei Shone Chen, Tzu Chen Lin, Jen Kou Lin, Pei Ching Lin, Shih Ching Chang. Clinicopathological and molecular differences in colorectal cancer according to location. *IJBM*2019, Vol.34(I):47-53.