REVIEW OF COLORECTAL CARCINOMA AND SPECIFIC DISEASE FEATURES IN THE POPULATION OF PAKISTAN

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ABSTRACT

Colorectal cancer is the solid cancer which may arise from the colon or the rectum with many similar features and may be referred to as colon cancer or rectal cancer depending upon the anatomical site of origin. It is one of the most common cancers and the leading cause of cancer related deaths in many countries. A significant rise in the incidence rate of the disease has been reported worldwide, especially in the countries of South Asia where the disease had a low incidence rate in the past. The clinical presentation of the colorectal cancer patient from this region is inclusive of young age and advanced disease stage. The awareness regarding the disease features and screening of the disease is scarce. This review provides a concise update on the pathological aspects of colorectal carcinoma and an insight on the clinical picture of the disease in the diverse population of Pakistan.

Keywords: Colorectal Carcinoma, Pakistan, Etiology, Prognostic Markers, Staging

INTRODUCTION

Colorectal cancer is the solid cancer which may arise from the colon or the rectum with many similar features and may be referred to as colon cancer or rectal cancer depending upon the site of origin. A million people around the globe develop colorectal carcinoma each year and half of these people usually die due to systemic disease within a span of five years from the time of diagnosis.[1,2] Colorectal carcinoma is hence regarded as the most common cause of cancer related death next to lung cancer, where many patients are presented with surgical resection stage but half of the presented cases are unable to survive from the disease.[3] The palliative therapy with radiation can be given in the patients. The chemotherapeutic therapy was not very promising in the past and resulted partial or infrequent shrinkage of tumor mass at high cost and less improvement in general status, whereas nowadays with the advancement of novel chemotherapeutic agents, the survival benefit and improvements in quality of life has been attained.[3] The pathological aspects of colorectal carcinoma is variable in different population groups in the developed and underdeveloped countries.

Risk and Etiological Factors associated with Colorectal Carcinoma

Colorectal carcinoma (CRC) in few cases may arise from genetic polyposis syndrome, but in most cases the source of origin is sporadic adenoma(65-85%) or Familial (10-30%).[4,5,6] CRC is usually a slow developing cancer which may arise from a polyp which is otherwise benign neoplasia. Hyperplastic polyps or inflammatory polyps do not change into cancer whereas adenomatous polyps may be pre cancerous.Familial adenomatous polyposis ,caused by APC gene mutations leads to 1% of CRC.[4,5]The risk factors are variable in developed and underdeveloped populations whereas besides genetic propensity and lifestyle , many dietry /fecal and colonic components may also play a role. It was concluded by Cheah et.al in an review on etiology of CRC that "bile acids are the most strongly implicated factor" in the etiology of CRC.[7] The Colorectal carcinoma may emerge as a complication of Crohn's Disease or Ulcerative Colitis (accounting 1-2% of all the reported CRC in general population).[8] The risk of colorectal carcinoma in patients of irritable bowel disease increases 0.5-1% each year and 8-10 years after diagnosis.[8] The risk of complication of IBD(irritable bowel disease) leading to CRC is higher in patients with early age irritable bowel disease diagnosis, severity and prolongation of symptoms(dysplasia and inflammation) and familial association.[5,9]The incidence of CRC related death in patients of inflammatory bowel disease is higher as compared to CRC than for sporadic associated disease.[10]Age and family history play a role in the incidence rate of CRC. It is rarely seen that CRC may occur in an individual below 50 years of age, whereas people with no family history of the disease are accounted

to be at an average risk level.[11]The risk of CRC in first degree relatives of CRC patients is two or three folds higher as compared to the general or control population.[11] Kune et.al reported in a case control study of dietary etiological factors of CRC that high fat intake and low milk intake serves as a high risk factor of CRC in both males and females, whereas beef intake serves as a risk factor in male patients only; whereas the intake of vitamin supplements was highly protective of CRC in both gender.[12] Melbourne Colorectal cancer study conducted to assess the possible correlation of CRC with chronic diseases, medications and operations reported that CRC is more frequently associated with hemorrhoids as compared to hypertension, arthritis stroke or chronic chest disease. Patients with type 2 diabetes are at a greater risk of CRC. A significant deficit in the disease in either gender was seen in people who utilized aspirin containing medicines and vitamin supplements.[13]Some syndromes due to genetic defects and mutations are also known to be specifically associated to CRC. HNPCC, referred to as Lynch syndrome (genetic defect in DNA repair) may also be the cause of 3-5% of CRC.[14] A rare inherited condition like Turcot Syndrome increases the risk of adenomatous polyps and Colorectal Carcinoma.[15] Hemartomas in patients of Peutz-Jeghers syndrome (mutation of gene STK11) can lead to an increases risk of CRC.[16] MUTYH-associated polyposis leads to CRC if the colon is not removed in these patients, which is caused by the mutation of gene MUTYH.[17]

Screening and Diagnosis of Colorectal Carcinoma

Genetic testing and screening should be done in people with no apparent symptom of CRC with strong family history or risk factors. Colorectal screening is both challenging and complex specially in populations with high incidence rate and economic instability due to lack of factors like awareness, patients acceptance and financial insurance, risk stratification, appropriate diagnosis, management and follow up. [18 , 11] The usual sign and symptom of CRC are changes in bowel habit, rectal bleeding, abdominal pain, distress and cramping, weight loss ,weakness ,lethargy or fatigue.[19]Before any apparent clinical symptoms, fecal blood can be detected in patients of CRC by stool test, occult blood tests and fecal DNA tests. endoscopic screening e.g. flexible sigmoidoscopy, colonoscopy helps in the detection, removal and biopsy of the polyps and thus referred to as Gold standard diagnostic procedures.[21,22] Radiographic screening procedures like computed tomographic colonography (CTC/virtual colonoscopy) , double contrast barium enema may have higher cost and a greater risk of subsequent exposure to ionizing radiation. Patients with abnormal barium enema test require colonoscopy for further diagnosis. CTC has high sensitivity and specificity for polyps 10 mm or larger whereas flat lesions are missed as a drawback.[23,24]

Histological classification, Grading, Staging and Prognostic markers of Colorectal Carcinoma

The diagnostic report of resected CRC specimen specifies the anatomical site of origin, histological type, parameters definite of local tumors and evidence of metastases.[25] It can very much predict the chances of survival or susceptibility of the disease to chemotherapy. Clinicopathological evaluation and quality control e.g the actual tumor size vs. the size assessment by imaging may be attained. The standardization and interpretative value of these diagnostic features are however variable.[25] To attain specific and consistent pathological report of CRC, the globally accepted standard histological classification is by WHO, [26,27,28] which classifies CRC into

a) Adenocarcinoma
b) Medullary Carcinoma (non gland forming carcinoma of uniform polygonal cancer cells infiltrated with lymphocytes and nested, organoid, trabecular pattern, referred to as undifferentiated carcinoma in the past-prognostically favourable)[25,29]
c) Mucinous (colloid) adenocarcinoma (50% mucinous) (serves as an adverse prognostic factor when located at rectosigmoid)[30]
d) Signet-ring cell carcinoma (50% signet-ring cells)(prognostically significant)[25]
e) Squamous cell (epidermoid) carcinoma
f) Adenosquamous carcinoma
g) Small-cell (oat cell) carcinoma(prognostically unfavourable)[25]
h) Undifferentiated carcinoma
i) Other (*e.g.*, papillary carcinoma)

The tumors in CRC are graded by different methods but the common gradings are as follows [25,33]

Grade 1 (Well differentiated),
Grade 2 (Moderately differentiated),
Grade 3 (Poorly differentiated),
Grade 4 (Undifferentiated)

or

Low Grade (Well differentiated and moderately differentiated)
High Grade (Poorly differentiated and undifferentiated)

The TNM system of staging the tumor of the AJCC and IUAC is the most recommended, standardized and accepted.[25,32-35]

Figure 1: Staging & Definitions according to AJCC/UICC TNM

Figure 2 : Groupings & Definitions according to AJCC/UICC TNM

The assessment of tumor stage has significant prognostic marker capability, however the search for an ideal biomarker ensues with the investigation of many proteins, molecular and carbohydrate markers but none have been yet validated in patients prognosis.[36] Thymidylate synthase (TS) is a chemosensitive marker. Thymidylate Synthase is the target enzyme of 5FU, which is utilized for DNA synthesis in the S-phase of the cell cycle. High TS levels are indicative of tumor relapse and TS levels may correlate with the degree of 5FU chemotherapeutic resistance.[37,38]DCC/18q LOH ,suppressor gene which is a putative tumor marker for adverse outcome such as shortened disease free and overall survival.[39,40] MSI-H is a Marker of Favorable prognostic Outcome correlated with increased survival rates of like stage tumors.[41,42] The putative biomarkers with prognostic significance in colorectal carcinoma are CD44 v6 , Mn superoxide dismutase ,Ki-ras, C-reactive protein, Bc1-2, Bax Vitamin D receptor, Hyaluronic acid, Thymidine phosphorylase ,PCNA, Plasminogen activator, P53/17p LOH, Chromosome 1 aneuploidy, UPA receptor P21 ,Chromosome 11 aneuploidy, Matrix metalloproteinases ,P27 Microsatellite instability, Cathepsin B, C-myc, TIMP ,HER2/ne, Si LeA ,VEGF ,NM23,Si LeX ,Thymidylate synthase, Ki67,CEA ,Prolactin, receptor Cyclin D1,Sucrase-isomaltase ,DCC/18q LOH, Ploidy.[25] The development of biomarkers assay techniques and valid analytical procedure is a lengthy and complex process with several pre-analytical and intra-analytical challenges.[43]
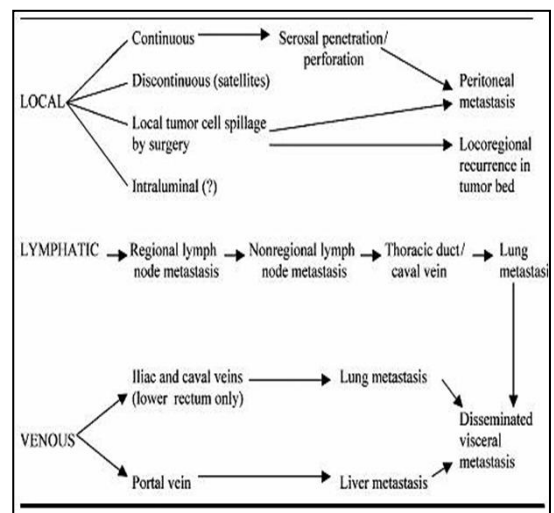
Figure 3: Pathways of cancer spread in colorectal carcinoma

Colorectal carcinoma in Pakistan:

Colorectal carcinoma is the third most prevailing cancer in men and second most prevailing cancer in women worldwide whereas the difference in the regional incidence rate is more than 10 -folds.[45] The highest incidence rate of colorectal carcinoma is reported in Eastern European countries, Japan, Australia, New Zealand and U.S Blacks

whereas comparatively lower rates are reported in Africa, Central and South America, India and Pakistan[46]. The actual number of cases of colorectal carcinoma in Pakistan which is the seventh most populous country in the world may be enormously varied as most of the cases leading to death by CRC go unreported and the precise incidence rate, mortality rate, number of new cases and deaths due to cancer annually are not known in Pakistan.[46] Pakistan faces an augmented burden of the disease due to economic strains and a rise in the incidence rate and risk factor profile of cancer each year.[47,48] To measure the cancer burden through a sample population in 1995, The Karachi cancer registry was established,[49] some radiotherapy institutes have also provided interrupted report of relative frequencies of different cancer.[50] In a report generated by Pakistan medical research council from data generated by six radiotherapy institutes between 1973-1974,colorectal carcinoma was ranked as the 6th carcinoma among the ten most prevailing carcinomas in Pakistani men with a incidence rate of 5.7%. The Karachi cancer registry reported a comparatively lesser incidence rate, 4.1% in men and the sixth most prevailing carcinoma in men, whereas CRC was reported to be the 9th most prevailing carcinoma in women with an incidence rate of 5%, in a population based study between1995-1999.[51] Although it is widely accepted that CRC occurs in males above 50 years of age and hence old age is regarded as one of the probable risk factor, a five years study in Pakistan has shown on the contrary that incidence of colorectal carcinoma predominantly in male patients under 60 years of age is more with higher occurrence of left sided lesions(tumors in distal locations are more than tumors in proximal subsites).[52] Young age of the patients of CRC at the time of clinical presentation has been reported in other studies on Pakistani population, Very advanced disease stage is presented in most patients with 5 years relative survival of less than forty percent of overall survival.[53]In the year 2005,the statistics by WHO in Pakistan has shown that CRC is the eighth leading cause of cancer related death in men and seventh leading cause of cancer related deaths in women.[54] The Annual cancer registry report in the year 2006 by Shaukat Khanum Memorial Cancer Hospital shows that breast carcinoma is the most prevailing cancer in adults followed by hepatocellular carcinoma, non Hodgkin lymphoma, oral cavity cancer and colorectal carcinoma.[55]

A study of six years in a tertiary care hospital of Sindh Pakistan reports that the rectal bleeding and pain were the predominant symptom of CRC followed by altered bowel habits in most patients whereas family history of the disease was not seen in any case unlike the data reported in west.[56] Half of the presented case were rectal and sigmoid tumors whereas well and moderately differentiated tumors were assessed in most patients. Ahmed et.al reported in a study based on histopathological assessment of colorectal resected specimens that the malignant tissues is presented with positive lymph nodes and extensions into pericolonic fat which shows the advanced disease stage .The study signifies the importance of early detection and surgical intervention with better surgical techniques at an early stage is largely required in the Pakistani population.[53]Soomro et.al reported in a recent study on colorectal patients (mean age 49.52±15.42) in Sindh, Pakistan that sigmoid was the most common anatomical site for CRC, most of the patients were presented with well differentiated histopathology of the cancer, the frequent clinical presentation was abdominal mass as the most common presenting symptom followed by bleeding per rectum, obstruction, abdominal pain and irregular bowel movement. Left hemicolectomy was the most employed surgical procedure.[57] Another recent study on clinical presentation of CRC in Pakistani patients below 40 years of age, conducted at a tertiary care hospital, Peshawar, Pakistan shows that the most common presenting symptom was altered bowel habit(86%) followed by weight loss(within a mean of four months) and abdominal pain(84%).The most frequent observed sign in these patients was anemia(72%) and jaundice(48%),edema feet(12%) and Lymph node(inguinal).Left sided tumors(70%) were more frequently present than right sided tumors(30%).[58] In the perspective extended by different population based studies, research and reports on colorectal carcinoma in Pakistan, it is correctly assumed that any study conducted on the population in Karachi would stand out as a study on sample population of Pakistan, because the population distribution in Karachi is similar to the population distribution in Pakistan with respect to ethnicity, race, age, gender and religion. Karachi South (southern most district of Karachi –population 1,724,915 a/c census 1998) is the distinctive district in Pakistan which represent each and every ethnic (Sindhis, Punjabis, Pathans ,Balochs and muhajirs) and socioeconomic population group of the country and is taken as the sample population of Pakistan to generate Karachi cancer registry.[59] The cases of CRC in Karachi reported in the year 1995-2002 indicate that the incidence rate of colorectal carcinoma is on a rise especially in men and is associated with younger age and advanced stage of the disease at the time of diagnosis in the unscreened general population. The aging population and the changes in lifestyle of the general population hold the risk of enhancing the incidence rate of the disease.[60] From a global viewpoint Karachi, Sindh falls in the low risk area of CRC (4.4%cases in males and 2.8% in females which is half of the global 9.4% cases).[60,61] Predominance in males of Karachi South is seen (1.7:1) for CRC and (2:1) for rectal cancers. In Karachi South the right sided colon cancer is more prevalent than the left side.[60] The investigations on implication of old age on the incidence rate of CRC in the population of Pakistan varies from the global reports which signify that old age is a valid risk factor for CRC specifically in males.[62,63] A retrospective review of pathological confirmed CRC patients in a leading tertiary care hospital in Karachi ,conducted to assess the implications of old age (using a cut of of 70 years) on the surgical complications reports that 75.6% of patients were of age group 70-88 and 50.1% of the patients were of age group 15-69 and older age is not independently correlated with the complications of surgery for CRC.[64] Another study clearly shows that CRC in Pakistan is associated with advanced disease stage at the time of diagnosis. [65]

CONCLUSION

Patients clinically diagnosed with colorectal carcinoma in Pakistan are presented with young age, subsided lesions and advanced stage of a progressive disease which leads to the added complications in surgical interventions and severe implications of chemotherapy. The fact that the disease is not diagnosed at an earlier stage accounts for factors like socioeconomic burden, lack of awareness and inadequate health care facilities. Focus should be laid on the initiation of screening of the disease and generation of relative awareness in the masses to contain the intricate scenario.

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