Original Article

Tumour sidedness and clinicopathological features of resected colon cancer in rural population of Northern Pakistan: single institutional analysis

Shah Zeb Khan (MD) [iD] [a,*], _Ismat Fatima_ [b]

[a] _Bannu Institute of Nuclear Medicine Oncology and Radiotherapy (BINOR), Department of Clinical Oncology, Bannu, Pakistan_
[b] _Institute of Nuclear Medicine and Oncology Lahore (INMOL), Department of Clinical Research, Lahore, Pakistan_

A R T I C L E   I N F O

A B S T R A C T

Objectives: Different clinicopathological and molecular features have been demonstrated between right and left sided colon cancers. We aimed to characterize colon cancer and sidedness among a North-Pakistani rural population diagnosed with colon cancer in our institution.

Methods: Seventy patients were included in the study that received adjuvant chemotherapy at Bannu Institute of Nuclear Medicine Oncology and Radiotherapy) Bannu, Pakistan from January 2014 to December 2017. Chi-square test was used for significance of categorical variables. p-Values less than 0.05 were considered significant.

Results: Mean age at diagnosis for right side colon cancer patients was 43.94 years and for left side colon cancer, it was 49.83 with no significant difference. Male patients were presented more with right (77% vs. 54%, $p = 0.044$) and females with predominantly left sided tumours i.e. (46% vs. 23%, $p = 0.044$). Right sided cancer tended to be more poorly differentiated (20% vs. 0%, $p = 0.020$). Mucinous adenocarcinoma was seen mostly in right sided colon cancer (37% vs. 3%, $p \leq 0.001$). There were more locally advanced presentation of right side colon cancer with more node positive (83% vs. 60%, $p = 0.025$) and lymphovascular invasion (51% vs. 37%, $p = 0.016$). Sigmoid colon was the most common tumour subsite involved.

Conclusion: Our study is the first report of colon cancer in a rural population in North-Pakistan. An earlier onset of tumours (44–50 years) was observed in comparison with global data.

* Corresponding author.
  E-mail: skhanizhere0@gmail.com (S.Z. Khan).

Lateralidade tumoral e características clínico-patológicas do câncer de cólon ressecado na população rural do norte do Paquistão: análise em uma única instituição

R E S U M O

Palavras-chave:
Lateralidade do câncer de cólon
Câncer de cólon no lado
esquerdo
Câncer de cólon no lado direito
Clínico-patológico
Rural

Objetivo: Características clínico-patológicas e moleculares distintas foram observadas em tumores de cólon no lado direito ou esquerdo. O presente estudo teve como objetivo caracterizar o câncer de cólon e sua lateralidade em uma população rural norte-paquistanesa diagnosticada com câncer de cólon nesta instituição.

Métodos: O estudo incluiu 70 pacientes que foram submetidos a quimioterapia adjuvante no Instituto Bannu de Medicina Nuclear Radioterapia Oncológica (BINOR), Bannu, Paquistão, entre janeiro de 2014 e dezembro de 2017. O teste qui-quadrado foi utilizado para mensurar a significância das variáveis categóricas. Valores de p menores que 0,05 foram considerados significativos.

Resultados: A média de idade ao diagnóstico entre pacientes com câncer de cólon no lado direito foi de 43,94 anos e entre aqueles com câncer de cólon no lado esquerdo, 49,83, sem diferença significativa. Os pacientes do sexo masculino apresentaram mais tumores no lado direito (77% _vs._ 54%, p = 0,044) e as pacientes do sexo feminino apresentaram mais tumores no lado esquerdo (46% _vs._ 23%, p = 0,044). Tumores mal diferenciados foram mais comumente observados no lado direito (20% _vs._ 0%, p = 0,020). Adenocarcinoma mucinoso foi observado principalmente em casos de tumores no lado direito (37% _vs._ 3%, p ≤ 0,001). A apresentação local estava mais avançada em tumores de cólon no lado direito, com mais linfonodos positivos (83% _vs._ 60%, p = 0,025) e invasão linfovascular (51% _vs._ 37%, p = 0,016). O cólon sigmoide foi o sublocal mais comum.

Conclusão: O presente estudo é o primeiro relato de câncer de cólon em uma população rural no norte do Paquistão. Em comparação com dados globais, observou-se um surgimento mais precoce dos tumores (44-50 anos).

Introduction

Colon cancer is the third most common cancer over the world and the second for mortality, with estimated 95,520 new cases and 50,260 deaths in 2017.[1] Differences between right and left sided colon cancer have been demonstrated, revealing epidemiological and clinicopathological peculiarities. Treatment algorithms have also been proposed on the basis of stage and laterality. Accordingly, inexpensive and widely applicable clinicopathological assessments for prognostic information are warranted to guide the clinicians to tailor the colorectal cancer treatments. Rightward shift of Colorectal Carcinoma (CRC) with increased prevalence in younger patients has been documented in recent years.[2,3]

Pakistan has no National cancer registry so cancer incidence and mortality data cannot be computed and only demographic-based estimations are available to picture the cancer burden in the country.[4] However, some reports are available from single institution case series. The Shaukat Khanum Memorial Cancer Hospital, Lahore reported 450 new cases of colorectal cancer in 2016, the second most commonly diagnosed malignancy.[5] Indeed, no specific molecular epidemiological data is available, often related to the unavailability of diagnostic tests for RAS proteins and mismatch-repair enzymes in low-middle income countries,

with disparities between urban and rural settings of care.[6] In Pakistan, 61% of the population resides in rural areas.[7] Here, data regarding colon cancer is completely missing, both for incidence, mortality, histotype and molecular evaluation. In general, a more common genetic hypermutability in colon cancer is described in right side colon cancer, resulting in Microsatellite Instability (MSI) phenotype.[8]

We conducted a mono-institutional hospital-based retrospective study to evaluate clinicopathological differences between resected right and left sided colon cancer in a rural Pakistani population, from Southern Khyber Pakhtunkhwa province.

Materials and methods

A manual research of consecutive medical records of the patients resected for colon cancer at Bannu Institute of Nuclear Medicine Oncology and Radiotherapy (BINOR) was performed between 1st and 30th June 2018. Patients belonged to rural areas of District Bannu, Karak, Lakki Marwat, D.I. Khan, Kohat and FATA. All patients included were 18 years or above.

It was a cross sectional observational study. We selected the patients treated with curative intention between January 2014 and December 2017, where a complete pathological report was available, inclusive of clinicopathological

characterizations. Cases of denovo metastatic cancer, biopsy of metastasis with no information of the primitive and autoptic reports were excluded. Patient was diagnosed either by colonoscopy and biopsy or emergency laprotomy due to acute abdomen symptoms, was done with resection of tumour. Histopathological diagnosis was considered on the postoperative surgical specimen; AJCC TNM 7th edition was used for staging. Post operative CT scan imaging was done in every patient.

The right sided colon cancer included all tumours located proximal to splenic flexure and those distal to it were part of left side colon cancer excluding rectosigmoid and rectal tumors.[9] Variables included in study were: age, laterality, pT stage, pN stage, histology type, Lymphovascular Invasion (LVI), Perineural Invasion (PNI) and grade. We considered 50 years of age as cut off to be considered as young patient as most medical literatures reported screening programmes from 50 years.

The study was approved by the institutional ethical committee of BINOR, Bannu, Pakistan.

Statistical methods

Data was analyzed using SPSS statistical software version 20.0. Mean was determined with standard deviation for age. Difference in mean was determined using independent sample t-test. Categorical variables were described in frequencies and percentages. Chi-square test was used for significance of categorical variables. p-Values less than 0.05 were considered significant.

Results

Patient characteristics

A total of 70 patients were included in the study. Demographics and clinicopathological data of all patients are summarized in Table 1. Mean age at diagnosis for right side colon cancer patients was 43.94 years (SD ± 19.29) and for left side colon cancer, it was 49.83 (SD ± 16.72) with no significant difference (p = 0.177). In female patients, left sided colon cancer was significantly higher than right side (46% vs. 23%, p = 0.044). On the other hand, right side colon cancer was involved in majority of the male patients (77% vs. 54%, p = 0.044) as shown in Table 1.

Tumour characteristics

Frequencies of various subsites of colon cancer are reported in Table 2. Sigmoid localization was the most represented (40%) followed by ascending colon (35.7%), descending colon (10%), cecum (10%) and transverse colon (4.3%) as shown in Table 2. Mucinous adenocarcinoma was seen mostly in right sided colon cancer than left side cancer (37% vs. 3%, $p \leq 0.001$). More signet ring histology in right side cancer was observed (23% vs. 6%, $p \leq 0.001$), the remaining proportion of patients had adenocarcinoma NOS (91% vs. 40%) as seen in Table 1.

Advanced stage presentation was more common for right side (stage III, 86% vs. 63%, $p \leq 0.001$), with more patients

were having pT4 tumour (p = 0.007) and node positive (pN1 or pN2 = 83% vs. 60%, p = 0.007) with LVI (51% vs. 37%, p = 0.016).

There was no statistically significant difference in perineural invasion among both sides (p = 0.80). However, report of perineural invasion and LVI was missing in 54% and 20% of patients, respectively. Moderately differentiated tumour was seen in 74% of right side cancer and 94% left side cancer. Poorly differentiated tumour was present only in right side cancer with statistically significant results (20% vs. 0%, p = 0.020).

Discussion

Our report analyzed a rural population from North-Pakistan, southern Khyber Pakhtunkhwa province. The mean age of the patients was less than 50 years in our study, significantly earlier than the average age for colorectal diagnosis in other previous published series in other countries.[10–12] A recent study in Pakistan showed that younger patients are diagnosed with colon, supporting our observation.[13,14] Unfortunately, no familiarity was assessed nor retrievable from our medical reports, not possibly excluding a familiar pattern of inheritance.

Male predominance was seen in our study with more females with left sided cancer than right sided, contrary to the other international non-Middle East specific reports[15,16] and in agreement with a recent Pakistani report, showing more females presenting with left sided cancer[17]; perhaps, this data must be interpreted with caution since our report considered transverse colon as right side and excluded rectal primitive tumours. These findings show that patient characteristics in our region differ from western populations, with possible prognostic implications and different algorithm and priorities of cancer management. Indeed, different risk factors may be involved.

Sigmoid colon was the most common subsite involved in left sided cancer while ascending colon in right side cancer. Previous studies also showed more cancers are seen in these subsites.[9,18,19] The most common histopathology seen in colon cancer is adenocarcinoma NOS,[8,10] with mucinous and signet ring adenocarcinoma commonly seen in right sided cancer. These findings remain consistent with published literature.[20,21]

No patients presented with Stage I or pT1 primitive tumour. All the patients presented in Stage II and Stage III, 74% (n = 52/70) staged as III. This shows that locally advanced presentation is common in our population, primarily due to lack of adequate referral systems and timely access to oncology care along with the total unavailability of a screening programme at population-level.

More locally advanced presentation was seen in right sided cancers, according to the delayed onset of symptoms.[22] pT4 stage was seen in right sided cancers more than their left side counterparts. These findings remain consistent with previous studies showing more aggressive nature and delayed clinical presentation of right sided cancers.[15,23] This resulted in more node-positive findings.[24,25] More lymphovascular invasion in right sided tumour is also shown in previous studies.[21,26] Due to lack of qualified histopathologists and standard pathology units, some specific findings were missing in reports,

Table 1 – Baseline characteristics.

Characteristic	Right colon n (%)	Left colon n (%)	p-Value
Age years (mean ± SD)	43.94 ± 19.29	49.83 ± 16.72	0.177
Gender			0.044
Female	8 (23)	16 (46)	
Male	27 (77)	19 (54)	
Histology			<0.001
Mucinous adenocarcinoma	13 (37)	1 (3)	
Signet ring adenocarcinoma	8 (23)	2 (6)	
Adenocarcinoma (NOS)	14 (40)	32 (91)	
Tumour stage			0.007
pT2	3 (8)	2 (6)	
pT3	9 (26)	22 (63)	
pT4	23 (66)	11 (31)	
Lymph node stage			0.025
pN0	6 (17)	12 (34)	
pN1	22 (63)	10 (29)	
pN2	7 (20)	11 (31)	
NA	0 (0)	2 (6)	
Stage grouping			<0.001
Stage II	5 (14)	11 (31)	
Stage III	30 (86)	22 (63)	
NA	0 (0)	2 (6)	
LVI			0.016
Yes	18 (51)	13 (37)	
No	7 (20)	18 (52)	
NA	10 (29)	4 (11)	
PNI			0.803
Yes	5 (14)	7 (20)	
No	10(29)	10 (29)	
NA	20 (57)	18(51)	
Grade			0.020
Mod diff.	26 (74)	33 (94)	
Poor diff	7 (20)	0 (0)	
NA	2 (6)	2 (6)	

especially LVSI and PNI. Mostly patients had moderately differentiated tumours and almost all of poorly differentiated tumours were seen in right sided tumours, in agreement with previous reports.[23,24,27]

The mean age seen in our patients was younger. Our population present mostly before 50 years of age, suggesting a possible hereditary aetiology or earlier and persistent exposures to known risk factors like physical inactivity, improper diet and smoking.[14] The earlier presentation is consistent with previous reports. A study in Saudi Arabia has documented that 63% incidence of CRC was observed in patients below 40 years.[2] Similarly, a decline in CRC incidence amongst older patients is observed in US but the rise is expected in younger patients ranging from 20 to 49 years till 2030. Possible causal factors include Type 2 diabetes mellitus, dietary changes during last decade including increased consumption of red meat and decreased use of fresh vegetables and fruits. Sedentary life style has also contributed in increased and incidence in younger ages.[12,28]

These data suggest the need for molecular and genetic testing in our population to identify the high risk population and treat accordingly. Interestingly, a recent position of the American cancer society suggested to start colorectal

Table 2 – Frequency of tumour subsite.

Subsite	Frequency	Percentage (%)
Cecum	7	10
Ascending colon	25	35.7
Transverse colon	3	4.3
Descending colon	7	10
Sigmoid colon	28	40

screening earlier, at 45 years of age in average risk population.[29] However, though limited, our small report suggests that a population-adapted screening schedule and timeline should be considered, supporting the urgent need to obtain reliable data from population, particularly in countries where a good quality registry is not in place.

The limitations of our study include the retrospective nature of the analysis, from a mono-institutional experience. Secondly, the study population was small and no RAS and MSI testing was available to refine the molecular typization. Data on follow-up are not available at this time of the data collection so no prognostic correlations were reported.

The study points out the need of a referral pattern for the timely diagnosis of colorectal cancer in rural Pakistan,

endorsing the recognition of warning signs in the primary care. Indeed, there is need for development of effective early diagnosis and navigation networks for the timely access to quality oncology care, optimizing the access to existing cancer services in a multidisciplinary environment; as a funding pillar, the development of national guidelines for referral, diagnosis and treatment should be supported, providing the best effective and cost-effective cancer interventions and prioritizing the health financial resources for an effective resource allocation to save as many lives as possible. There are no screening programmes for our rural population and cancer-referral delay is mainly due to lack of specialized units and high rates of illiteracy with low awareness for cancer risk factors control. Further studies will be needed to analyze the significance of laterality of colon cancer in Pakistani population, focusing on the molecular differences with a prognostic and predictive value. The development of National cancer registry should be supported on priority basis, ensuring more studies on colon cancer.

Conclusions

This is the first study, to our knowledge, conducted in a rural population in Pakistan. The study showed that clinicopathological differences exist between right and left sided colon cancers, possibly implying a prognostic significance. Further studies will be needed to analyze the significance of laterality of colon cancer in Pakistani population, focusing on the molecular differences with a prognostic and predictive value.

Conflicts of interest

The authors declare no conflicts of interest.

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