Original Article

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

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A R T I C L E   I N F O

Article history:
Received 11 March 2019
Accepted 7 May 2019
Available online 3 June 2019

Keywords:
Colon cancer sidedness
Left sided colon cancer
Right sided colon cancer
Clinicopathological
Rural

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 ≤ 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.

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https://doi.org/10.1016/j.jcol.2019.05.007
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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

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 linfvascular (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).

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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. 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 clinico pathological 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.

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. 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. 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. In Pakistan, 61% of the population resides in rural areas. 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.

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 de novo metastatic cancer, biopsy of metastasis with no information of the primitive and autop
tic reports were excluded. Patient was diagnosed either by
colonoscopy and biopsy or emergency laparotomy due to acute
abdomen symptoms, was done with resection of tumour.
Histopathological diagnosis was considered on the postopera-
tive 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. 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 com-
mittee of BINOR, Bannu, Pakistan.

Statistical methods

Data was analyzed using SPSS statistical software version 20.0.
Mean was determined with standard deviation for age. Dif-
fERENCE 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 cat-
egorical variables. p-Values less than 0.05 were considered
significant.

Results

Patient characteristics

A total of 70 patients were included in the study. Demograph-
ics 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 sig-
nificantly 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 ≤ 0.001).
More signet ring histology in right side cancer was observed
(23% vs. 6%, p ≤ 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 ≤ 0.001), with more patients
were having pT4 tumour (p = 0.007) and node positive (pN2 = 83% vs. 60%, p = 0.007) with LVI (51% vs. 37%, p = 0.016).

There was no statistically significant difference in perineu-
ral 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, signifi-
cantly 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 Unfor-
nately, 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 reports15,16
and in agreement with a recent Pakistani report, showing
more females presenting with left sided cancer17; 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 charac-
teristics 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.10,21

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 pre-
sentation 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 pro-
gramme 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 pathol-
ogy units, some specific findings were missing in reports,
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 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,

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Right colon n (%)</th>
<th>Left colon n (%)</th>
<th>p-Value</th>
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<td>Age years (mean ± SD)</td>
<td>43.94 ± 19.29</td>
<td>49.83 ± 16.72</td>
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<tr>
<td>Gender</td>
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<tr>
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<td>8 (23)</td>
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<td>27 (77)</td>
<td>19 (54)</td>
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<tr>
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<tr>
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<td>8 (23)</td>
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<td>Adenocarcinoma (NOS)</td>
<td>14 (40)</td>
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<th>Subsite</th>
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<tr>
<td>Ascending colon</td>
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<tr>
<td>Sigmoid colon</td>
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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.

Acknowledgement

We thank Dario Trapani, MD, School of Medical Oncology of University of Milan and European Institute of Oncology, Milan, Italy, for the editorial assistance, providing a support in reviewing the manuscript.

REFERENCES


