Original Article

Management and Outcome of Colorectal Cancer in a Resource-Limited Setting: Ahmadu Bello University Teaching Hospital, Zaria, Nigeria

H Theyra-Enias, N Tumba[1], OB Popoola[2]

Department of Radiology, Oncology Unit, Barau Dikko Teaching Hospital, Kaduna, [1]Department of Radiology, Bingham University, Plateau, [2]Department of Oncology, Federal Medical Centre, Jabi Abuja, Nigeria

Background: Colorectal cancer (CRC) is one of the most common malignancies seen in the Western World. It is increasing in developing countries due to adaptation of the western lifestyle with an incidence of 6% in Nigeria. Treatment options are dependent on the stage of disease at presentation, the performance status of the patient, and increasingly the molecular makeup of the tumor. There is a dearth of data on the treatment options obtainable for the management and outcome of CRC cases in Northwestern, Nigeria. **Aim:** The study assessed the treatment options and outcome of colorectal cancer patients in a tertiary institution, in Northwestern, Nigeria over a 10-year period. **Patients and Methods:** Between January 2006 and December 2015, data of one-hundred and twenty-two histologically confirmed colorectal cancer cases seen at the Surgery, Radiotherapy and Oncology Departments, ABUTH Zaria, were retrieved retrospectively from the case files and treatment cards of the patients at the health information unit of the hospital. The stage at disease presentation, treatment received, and outcome were analyzed. **Results:** Nearly a quarter of the patients fell within the age bracket 31–40 years with the median age being 41 years. While only 41% of the patients had their disease staged, 30.4% of the patients presented with advanced disease (Dukes'C + D). Only 95 cases received a form of surgery or the other. Colostomy however accounted for 28.4%. Eighty-nine of the patients received chemotherapy either as neoadjuvant, adjuvant or with palliative intent. External beam radiotherapy either with radical or palliative intent was received by 60 patients (49.2%). At 1-year follow-up sixty cases had been lost to follow up, and thirty-six cases had defaulted on one form of treatment. **Conclusion:** The study showed that stage at presentation and the available treatment options in the hospital informed treatment offered to the patients. However, surgery was readily performed due to the pattern of presentation and most patients benefited from just a diverting colostomy. Majority of the patients presented with rectal tumor which required radiotherapy as part of its treatment modality, although this is still a luxury in this part of the world. Chemotherapy is also readily available and often prescribed. Cost and limited facility for biomarker (K-ras) testing restrict the use of targeted therapy. Outcome at 1-year follow-up was poor with whereabouts of nearly half of the patients unknown.

KEYWORDS: *Chemotherapy, colorectal cancer, Nigeria, radiotherapy, surgery, treatment outcome*

Address for correspondence: Dr. H Theyra-Enias, Department of Radiology, Barau Dikko Teaching Hospital, P.O.BOX 9727, Lafiya Road, Kaduna, Kaduna State, Nigeria. E-mail: deezatheyra@gmail.com

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INTRODUCTION

*A*ccording to GLOBOCAN 2020 estimates of the worldwide burden of cancer, colorectal cancer ranked the third in terms of incidence (1.9 million cases; 10.0%) second in terms of mortality (935,000; 9.4%) in both sexes.[1] In Nigeria, it is the fourth most common cancer accounting for 6% of cases.[1] The disease can be considered a marker of socio-economic development and in countries undergoing major development transition, incidence rates tend to rise uniformly with increasing human development index.[1] Treatment of colorectal cancer is based on multidisciplinary approach dependent on accurate staging and histopathology, the performance status of the patient, and increasingly the molecular makeup of the tumor.[2,3] Surgical management is the primary treatment of potentially curable colorectal cancer.[4]

According to the National Comprehensive Cancer Network (NCCN) guidelines, early-stage colon cancer (stage 1 and 2) can be treated with surgery alone while observation or adjuvant therapy using chemotherapy is reserved for patients with high-risk factors for recurrence.[5] For Stage III disease, surgery with adjuvant combination chemotherapy is recommended.[5]

In developed countries, 70%–80% of newly diagnosed cases of colorectal cancer have localized disease that is amenable to curative surgical resection.[6] For the remaining 20%–30% of newly diagnosed patients who present with unresectable metastatic disease, systemic therapy is usually advocated and a growing list of factors are considered when choosing therapies for each patient.[6] Factors being considered include the goals of treatment, type and timing of prior therapy, different efficacy and toxicity profiles of the regimens, *KRAS* and *NRAS* mutational tumor status, and patient's co-morbidities and preferences. MSI status and location of the primary tumor were recently added as additional considerations.[5]

In addition, a considerable proportion of patients (40%–50%) experience disease recurrence after surgical resection or develop metastatic disease, typically in the liver or lungs.[5]

For patients with rectal cancer, multimodal treatment consisting of various combinations and sequences of surgery either endoscopically or by a trans-anal procedure [Trans-anal excision or Trans-anal Endoscopic Microsurgery (TEM)], chemotherapy, and radiation therapy are the mainstay of current therapy. For locally advanced diseases, neoadjuvant chemo-radiation has been widely used as a standard treatment protocol.[7,8]

Adhering to evidence-based guidelines of stage-based therapy leads to improved outcomes.[9]

With the recent rise in colorectal cancer cases, assessing and knowing the treatment options available and outcome of colorectal cancer patients in a tertiary facility is necessary to proffer solutions/policies that will bring about change in the current state.

There is a dearth of data on the treatment options obtainable for the management of colorectal cancer cases in Nigeria.

METHODOLOGY

Study design and setting

This is a descriptive study carried out by retrospectively looking at the case files and treatment cards of one-hundred and twenty-two histologically confirmed cases of CRC patients who presented to and were managed at Ahmadu Bello University Teaching Hospital, Zaria within a 10-year period (January 2006 to December 2015).

Ahmadu Bello University Teaching hospital is a 500-bed tertiary care institution located in Zaria city, Kaduna State, Northwest Nigeria.

The hospital serves Kaduna state and its environs with a catchment population of approximately 6 million people; it is also a major referral center for patients from all over Nigeria due to the availability of radiotherapy services.

The hospital has an oncology department, which provides curative treatment such as chemotherapy, radiotherapy and also palliative services for all histopathologically proven cancers. The Surgery department is divided into various subunits with gastrointestinal unit offering open surgeries and some chemotherapy services.

Study population

All patients with colorectal cancer irrespective of age who were diagnosed and managed in this center within the 10-year period were included. Diagnosis is usually confirmed after an endoscopic or exploratory laparotomy with biopsies taken. At diagnosis baseline hemogram, renal and liver function tests, retroviral screening, abdominopelvic ultrasound, and chest radiographs were routinely performed. Barium enema, CT chest abdomen and pelvis, and carcinoembryonic antigen level were occasionally performed.

Patients' details were retrieved from the files/ case notes and treatment cards in the health information unit. Information collected include patients' demographics (age, sex), stage at diagnosis, co-morbidities, site of disease, treatment modalities

received including- type of surgery done, chemotherapy schedule, targeted therapy, radiotherapy dose/fractions received, and outcome at 1 year after the presentation to the facility.

Recurrence and disease progression were confirmed by physical examination, imaging studies, and endoscopic examination with biopsy.

Inclusion criteria

All patients histopathologically proven as colorectal cancer irrespective of age were included.

Exclusion criteria

Patients without a histological diagnosis of colorectal cancer were excluded.

Non-cancerous and other benign colorectal lesions were also excluded.

Definition of variables

The Dukes staging was referenced for staging as follows:

DUKES' A- Cancer limited to the rectal wall, no extrarectal spread, no lymph node metastasis.

DUKES' B- Cancer extends into perirectal tissues, no lymph node metastases.

DUKES'C- Metastases are present in the lymph nodes

DUKES' D- Distant metastases

Anatomical sites of colorectal cancer

Right-sided tumors- cecal, ascending colon, hepatic flexure, and transverse colon.

Left sided- splenic flexure, descending colon, and sigmoid colon.

Rectal- rectosigmoid junction and rectum.

Recurrence was defined as evidence of new lesions after a year of undetectable disease following initial treatment.

Progression was defined as appearance of new lesions or spread while on treatment.

Defaulted treatment- Defined as patients' refusal, decline, delay or discontinuation of cancer treatment.

Loss to follow up- Defined as patients' who missed scheduled follow-up visits and their whereabouts were unknown.

Statistical analysis

Data collected were analyzed using SPSS computer software version 21.0 (SPSS, Inc. Chicago, IL, USA).

Descriptive analysis was carried out in the form of frequency and percentage tables for categorical variables. Continuous variables were summarized using mean, median, and standard deviation.

Ethical consideration

Ethical approval for this study was obtained from the ethics committee of Ahmadu Bello University Teaching Hospital before commencement of the study.

RESULTS

Treatment modalities

Thirty-six patients (29.5%) received a combination of surgery, sequential chemotherapy, and radiotherapy [Table 1].

Colostomy was the most frequent type of surgical procedure performed, accounting for 28.4% of cases, followed by Abdomino-perineal resection which accounted for 22.1% [Table 2].

- CAPOX- CAPECITABINE AND OXALIPLATIN
- IROX- IRINOTECAN AND OXALIPLATIN
- FOLFIRI- 5FU, FOLINIC ACID AND IRINOTECAN
- FOLFOX-5FU, FOLONIC ACID AND OXALIPLATIN
- GEMOX- GEMCITABINE AND OXALIPLATIN.

5FU, Leucovorin was the most common chemotherapy regimen used in 31.5% of cases [Table 3].

A total of 89 patients received chemotherapy either as monotherapy or combination therapy, the most common regimen being 5FU/LEUCOVORIN, which was given to

Table 1: Modalities of treatment

Modalities of treatment	Frequency (%) *n*=122
Surgery alone	20 (16.4)
Surgery + Chemotherapy	27 (22.1)
Surgery + Sequential Chemotherapy + Radiotherapy	36 (29.5)
Surgery + Concurrent Chemo-radiation	12 (9.8)
Radiotherapy alone	12 (9.8)
Chemotherapy alone	14 (11.4)
Supportive/Palliative care	1 (1)

Table 2: Distribution of Patients according to the type of Surgical procedure performed (*n*=95)

Surgical procedure performed	Frequency (%) *n*=122
Colostomy	27 (28.4)
Abdomino-perineal resection	21 (22.1)
Right hemicolectomy	15 (15.8)
Left hemicolectomy	12 (12.6)
Anterior resection	10 (10.5)
Exploratory laparotomy + colostomy	9 (9.5)
Ileostomy	1 (1.1)
Total	95

Table 3: Schedule of chemotherapy and radiotherapy

	Frequency (%)
Type of chemotherapy	
Neoadjuvant treatment	29 (32.6)
Adjuvant treatment	44 (49.4)
Progressive disease	11 (25)
Recurrent disease	4 (9.1)
Palliative	16 (18)
Chemotherapy regimen	
5Fu, Leucovorin	28 (31.5)
Folfox 4	15 (17.0)
Capox	10 (11.2)
Single agent capecitabine	8 (9.0)
Irox	6 (6.7)
Capox, irox	6 (6.7)
Folfiri	4 (4.5)
Folfox 4, capecitabine	4 (4.5)
Folfiri, capecitabine	3 (3.4)
Irox, capecitabine	2 (2.2)
Folfox 6	1 (1.1)
Gemox	1 (1.1)
Single agent oxaliplatin	1 (1.1)
Total	89
Schedule of Radiotherapy	
Neoadjuvant concurrent chemo-radiation	5 (8.3)
Adjuvant	38 (63.3)
Concurrent chemo-radiation	7 (11.7)
Sequential radiation	31 (51.6)
Palliative	17 (28.3)
Total	60

Table 4: Schedule of radiotherapy

Dose	No of fractions	Number of patients	TOTAL
15 Gray	3#	2	9 Patients
	5#	7	
20 Gray	4#	1	8 Patients
	5#	5	
	10#	2	
45 Gray	15#	1	15 Patients
	25#	14	
46 Gray	23#	1	1 patient
46. 8 Gray	26#	1	1 patient
48 Gray	24#	2	2 Patients
50 Gray	25#	13	13 Patients
50.4 Gray	28#	2	2 Patients
54 Gray	27#	8	8 Patients
56 Gray	28#	1	1 Patient
TOTAL		60 Patients	60 Patients

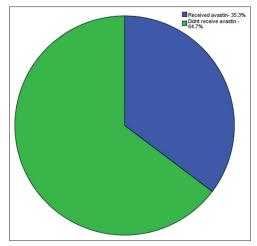28 patients (31.5%), followed by FOLFOX 4 given to 15 patients (17.0%).

Figure 1: Pie chart of the distribution of patients who required Bevacizumab

Seventeen patients with metastatic disease required Bevacizumab (Avastin), which was prescribed but only 6 patients (35.3%) received it [Figure 1].

A total of 60 patients (49.2%) received radiotherapy ranging from as low as 15 Gray in3 # to 56 Gray in 28# [Table 4].

At 1 year follow up nearly half (49.2%) of the cases had been lost to follow up [Table 5].

DISCUSSION

Colon and rectal cancers though commonly grouped together because of their origin are two separate cancers requiring different treatment approaches.[10] Appropriate diagnosis and staging are crucial to ensure a correct treatment strategy. Guidelines such as the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) have been developed to standardize the care of patients and are mostly used by physicians to aid in treatment decisions.[11] Oftentimes local special characteristics of our healthcare system could make total adherence to guidelines difficult and as such some inconsistency when managing such patients.[12]

In the last 10 years, the mortality rate of CRC has decreased by more than 20% due to the rising developments in diagnostic techniques and optimization of surgical, adjuvant, and palliative therapies.[13]

In this study, only 41% of the patients had their disease staged; a significant number 30.4% of the patients presented with advanced disease (Dukes'C + D), which is similar to data published by Kumar *et al*. in Oman.[14] Hence, the type of treatment received was determined by the stage.

Table 5: Outcome of patients at 1 year

Outcome at 1 year	Frequency (%)
Alive on follow-up	9 (7.4)
Dead	17 (13.9)
Defaulted treatment.	
While on 1st line chemotherapy/EBRT	36 (29.5.)
Radiotherapy machine breakdown	8 (6.6)
No reasons	5 (4.1)
Lack of funds	4 (5.7.)
2nd line chemotherapy due to side effects	7 (3.2)
Deterioration of symptoms	5 (4.1)
Progressive disease declined recommended treatment	3 (2.5) 3 (2.5)
Recurrent disease	1 (0.8)
Lost to follow up	60 (49.2)
Total	122

Surgery represents the mainstay of treatment in early cases but oftentimes patients are primarily diagnosed at an advanced stage occasionally with distant metastases resulting in poorer treatment outcomes for these patients.[13,15]

A combination of ignorance, high cost of medical care, biologically more aggressive disease could be ascribed as causes of late presentation and advanced stage, which is usually associated with unfavorable prognosis in Africa.[16] The late presentation can also be attributed to a lack of education on the signs and symptoms of colorectal cancer among the populace, the absence of specific screening programs for early detection, and the fact that most people might be unaware of the importance of reporting early to hospital for diagnosis and treatment.[17]

Considerable evidence exists that screening of asymptomatic persons who are at average risk can detect cancers early and at a curable stage, resulting in a reduction in mortality.[18] Furthermore, some screening tests may also detect cancer-precursor lesions, which if removed will result in a reduced incidence of colorectal cancer.[13]

Complete resection of colorectal cancer with resection of adjacent lymph nodes is the only chance for cure in early-stage cancer. However, most of the patients we see in our environment present with advanced disease at the time of diagnosis, for which only palliative surgery (colostomy) is possible.[13] As seen in our environment, the majority of the patients benefited from a diverting colostomy. ABUTH, being a tertiary institution that provides radiotherapy service facilitates referral for neoadjuvant and adjuvant treatment. Surgery

was performed in 77.9% (*n* = 95) of cases; the most common surgical procedure performed was colostomy 22.1% (*n* = 27), which was due to advanced stage of presentation to relieve intestinal obstruction. This is comparable to a study in Iraq where palliative colostomy for cancer of the rectum is common.[19]

The location of the tumor and stage at presentation determined the type of surgery done. 17.2% (*n* = 21) had abdomino-perineal resection (APER) because there were more left-sided tumors than right-sided tumors, which is similar to the finding by Irabor *et al*. in Ibadan, Nigeria with a 2:1 rectum to colon ratio; thus more APERs were performed.[20] This is also comparable to the review done by Wismayer in East Africa where APERs were performed in 54%–71% of cases due to advanced stage of presentation of rectal tumors.[21] However, the study by Sharma *et al*.[22] in Southwest Nigeria documented right hemicolectomy (31.7%) and diverting colostomy (30.3%) as the most common surgical procedures. Of the 20 (16.4%) patients who had only surgery, adjuvant therapy was recommended for 7 of them but they defaulted due to lack of funds, which only may support that Poverty may be a contributing factor to poor prognosis.

Adjuvant chemotherapy and radiotherapy have been demonstrated to improve overall disease-free survival in selected patients with locally advanced disease in large intestine malignancies.[23]

Worldwide there is a shortage of radiotherapy services with over 90% of cancer patients in low-income countries lacking access to radiotherapy services.[24] In comparison with the high-income countries, where there is 1 megavoltage linear accelerator per 250,000, in Africa there is less than one teletherapy machine to one million people and Nigeria has 1 accelerator per 25.7 million, a 100-fold difference.[25,26] However, despite low availability 20% (*n* = 12) patients received concurrent chemo-radiation, either as neoadjuvant (*n* = 5) or adjuvant (*n* = 7).

Neoadjuvant radiation therapy is becoming quite popular but not readily used because of the limited number of radiotherapy machines in the country and long waiting list as such only *n* = 5 received neoadjuvant concurrent chemo-radiation, which concurs with Dares Salam in Tanzania East Africa whereby neoadjuvant radiation therapy is not popular, unlike in developed countries where it is offered to more than half of the patients.[19]

More than a quarter of these patients 29.5% (*n* = 36) received sequential radiotherapy after chemotherapy due to the long waiting list. Altogether 60 patients received radiotherapy using Cobalt machine, which

was the available machine in that center with doses ranging from 15Gy in 3# to 56Gy in 28#. The lower radiation dose (15Gy-20Gy) was administered to only 9.8% (*n* = 12) mostly for palliative purposes like pain control, bleeding, and bone metastasis; the higher doses (45Gy-56Gy) were mostly for radical treatment.

At the time of taking data for this study, this center was one among the three with a functional radiotherapy machine out of the eight available centers. The current standard of radiotherapy treatment is a 3-dimension conformal radiotherapy (3DCRT); this technique allows localization and dose calculation of the target volume and organ at risk (OARs) via 3D planning and dose volume histograms.[27]

In most developed countries, 3D radiotherapy and treatment planning is used; however, in Africa, most of the radiotherapy department deliver palliative and simple curative services using two-dimensional imaging and treatment planning, with just about 2% of centers equipped with modern imaging equipment and treatment planning software.[25] Presently there are a total of seven linear accelerators available in four centers in the country where 3D treatment planning is being used.[28] The majority of cancer patients would require radiotherapy to the primary and/or metastatic sites of which a cobalt 60 machine only makes it impossible to implement radiotherapy protocols to the standards available in developed countries.[29]

Colorectal cancer is a disease where several chemotherapeutic agents could be used either as monotherapy or combination therapy. 73% (*n* = 89) received chemotherapy ranging from single agent capecitabine, single agent Oxaliplatin, 5FU/Leucovorin, FOLFOX4, FOLFOX6, FOLFIRI, CAPOX and IROX. Most of the patients 31.5% (*n* = 28) received 5FU and Leucovorin, which were used mostly in the early years between 2005–2008 due to affordability and availability of the chemotherapeutic agents as most patients pay out of pocket with no health insurance scheme to cover cost, the next most used combination was FOLFOX 4 18% (*n* = 16). This is in contrast to the finding by Alatise *et al*. and Sharma *et al*. in Southwest Nigeria where FOLFOX was the most commonly used regimen.[22,30] The reason for this disparity would be the timing of data collection; our data was collected between 2005–2014, while theirs was collected between 2013–2016, when the use of FOLFOX had gained more grounds as against the use of 5FU and Leucovorin regimen.

A total of 17 cases had metastatic disease and required a monoclonal antibody (Bevacizumab), which was prescribed. Only 6 cases (35.3%) received it ranging from a single course to six courses. Eleven cases (64.7%) did not have it due to the cost of treatment.

Cetuximab could not be prescribed to patients due to lack of biomarker (K-ras) testing as of when data was taken. Of recent, there are available labs that conduct MSI/K-RAS testing.

At 1-year follow-up about half of the patients (*n* = 60) were lost to follow up, depicting a major challenge in Sub-Saharan Africa. Yawe *et al*.[31] in Maiduguri, Northeast Nigeria also noted very poor follow up with majority defaulting treatment after completion of adjuvant therapy; only 27% were on follow-up at 6 months. In this study, only 7.4% were alive and on follow-up, which is in keeping with Chayla *et al*.[18] who recorded a follow-up of 3–61 months among survivors, with 34 (11.4%) and 15 (5.1%) out of 332 patients available for follow-up at 6 months and 2 years, respectively. Being a retrospective study, we could not ascertain why some of the patients defaulted treatment and others lost to follow up. As seen in other studies, the true condition of these patients is difficult to ascertain due to attrition.[22,32,33] Some of the reasons recorded in this study were financial burden on patients and caregivers, deterioration of symptoms, machine breakdown, and side effects of therapy. Reasons from similar studies were lack of caregivers to assist patients to the health facility, travelling long distances, accommodation at the referral hospital, improvement in symptoms with a few courses of therapy, and belief in alternative treatments.[31,34] Those with progressive/recurrent disease did not receive the recommended treatment, with no reasons documented.

The limitation of this study was its retrospective nature; as a result, some information about patients were missing. Lack of patient navigators and funds to follow up patients who did not attend scheduled visits or those who did not adhere to treatment schedule to determine their true state was a major limitation.

CONCLUSION

The dreadful effect of late presentation is depicted in this study as most patients could not benefit from curative surgery. Colorectal cancer screening is an important component of prevention and early detection as this plays a major role in early diagnosis and improved clinical outcomes.

The study showed that treatment was dependent on what was available while trying to follow guidelines. Radiotherapy, which plays a major role in the

management of rectal cancer, is still a luxury in Nigeria as few centers offer this service. Concurrent chemo-radiation was possible in only a few patients with many benefiting from sequential chemotherapy than radiotherapy due to long waiting list with attendant machine breakdown.

Policies aimed at making molecular testing compulsory and affordable are a welcomed development; improving screening programs and cost-effective treatment will improve outcome in this environment.

The importance of patient navigators and patient tracking cannot be overemphasized as reasons why patients are lost to follow up should be properly investigated.

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Conflicts of interest
There are no conflicts of interest.

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