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Original Research

Dying Undiagnosed: Challenges of Management of Ovarian Tumours in a Resource-Poor Setting in North-western Nigeria

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Abstract

Background: Ovarian cancer is the second most prevalent but most lethal gynaecologic malignancy in our institution. This study aimed at determining the rate of non-diagnosis in suspected lesions and reviewing the management challenges of ovarian tumours highly suspicious for malignancy in our hospital.

Methodology: A three-year retrospective review of patients' records from the ward, clinic, theatre, and histopathology laboratory was carried out. Cases with high indices of suspicion for ovarian cancer (ovarian tumour with malignant radiologic features with any of ascites, pleural effusion, as well as cachexia, anaemia, or evidence of metastasis) were included. In-depth interviews were carried out with a consultant from each specialty of Radiology, Radio-oncology, Pathology, and Gynaecologic oncology at the gynaecologic oncology multidisciplinary team meeting.

Results: One hundred and twenty-two cases of highly suspicious ovarian malignancies were seen with a mean age of 40.6 years. Of these, 28 (23%) had surgery and 77% did not have any form of histological diagnosis. Of those that had surgery, 13 (46.4%) had upfront surgery and 15 (53.6%) neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS). Only two cases had documented complete (R_0) debulking. Among those that had upfront surgery, one case (7.7%) was an ovarian fibroid and one (7.7%) was a fibrosarcoma while two cases (15.4%) were borderline ovarian tumours. Chemotherapy was commenced based on malignant cells on ascitic or pleural fluid cytology in three cases. Of all the malignant cases, epithelial carcinomas were commonest accounting for 48%. Aside from the general late presentation of cases, insufficient funds for treatment, poor coverage of health insurance for cancer care, unavailability of routine immunohistochemistry, lack of germline and somatic testing, non-availability or prohibitive cost of some chemotherapeutic agents, unavailability of maintenance therapies, inadequate capacity to manage toxicities, inadequate skill across all specialties, unavailability / erratic function of computerized tomography scans and unavailable positron emission tomography, lack of interventional radiology facility amongst others were all identified as challenges to management.

Conclusion: Most patients with tumours highly suspicious for ovarian cancers did not get a histologic diagnosis and probably died undiagnosed. Management of ovarian cancer remains a challenge despite advances in surgical and chemotherapeutic options. Health insurance for all, infrastructure development, and training of all disciplines involved is recommended.

Keywords: Ovarian Tumours; Diagnosis; Undiagnosed Ovarian Tumors; Histology; Nigeria.

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Introduction

Globally, ovarian cancer (OC) is a highly lethal disease. In Nigeria, it is the second most common and most lethal gynaecologic cancer with 72% case fatality in 2020. [1] With 3,203 histologically confirmed cases from Ibadan, Ekiti, Abuja, and Calabar cancer registries in the 2020 Global Cancer Observatory (GLOBOCAN) statistics report, ovarian cancers were the fourth most common accounting for 4.4% of all female cancers. [1] Its high fatality could be as a result of its early stage being asymptomatic or lack of an acceptable screening method which is responsible for the late presentation in advanced stages with the consequent poor prognosis. [2] The common screening tools considered are transvaginal ultrasound and serum CA-125 levels. Both have the disadvantage of high false-positive rates leading to unnecessary interventions. According to the randomized controlled trials on ovarian cancer screening, screening did not lead to any significant reduction in mortality. [3] As such, because of the negative net benefit and risk ratio, it is not recommended to screen asymptomatic high-risk women.

For every woman that presents with an adnexal mass in our centre, a two-phase process is used to exclude malignancy. The first phase involves a detailed medical history, physical examination, imaging studies, and laboratory evaluation of tumour markers. The first imaging of choice is the pelvic ultrasound. [2] In a large meta-analysis, pelvic ultrasound is first-line imaging with a sensitivity and specificity of up to 91% and 83%. [2] The International Ovarian Tumour Analysis (IOTA) and Ovarian-Adnexal Reporting and Data System (O-RADS) may be used for the characterization and risk stratification of adnexal masses. [4]

Second imaging like Computerized Tomography (CT) scan or Magnetic Resonance Imaging (MRI), though frequently requested in our institution, may only be necessary if the gynaecologist cannot determine if surgical evaluation is necessary with the pelvic scan. Tumour markers should be sought in all postmenopausal or premenopausal women with ultrasound features suspicious of malignancy. The tumour markers requested in our institution depend on the clinical suspicion of the type of tumour but usually include Cancer Antigen-125 (CA-125), carcinoembryonic antigen (CEA), alpha fetoprotein (AFP), lactate dehydrogenase (LDH), Inhibin, Estradiol, and beta-human chorionic gonadotrophin (BHCG). Malignancy is suspected based on age, menopausal status, risk factors, elevated tumour markers, and imaging findings consistent with malignancy (solid components [most significant feature], thick septations, colour uptake in the solid component, presence of ascites and peritoneal masses). [2] If malignancy is suspected based on these (amongst other reasons), the second phase procedure is an abdominopelvic surgical exploration in order to stage, and obtain a specimen for histology, et cetera. In a randomized trial of 570 women who underwent surgical evaluation for suspected ovarian cancer only 5% was malignant. [5]

In suspected advanced cases, however, more imaging like Computerized Tomography scans of the chest, abdomen, and pelvis (CT-CAP) is done to assess metastases. When surgery is decided, the patient's ability to tolerate the surgery is assessed using various means. She is reviewed for any medical conditions, stabilized, and certified fit for the surgery by different subspecialists when indicated such as the cardiologist, anaesthetist et cetera. When a patient is not for surgery (due to the likelihood of non-resectability of tumour, disease in the portahepatis and liver or pulmonary metastasis, severe medical conditions et cetera), an image (CT or ultrasound) - guided biopsy should be done on peritoneal carcinomatosis or omental cake, which provides a site-specific diagnosis in 93% of patients [6] but this is rarely done in our centre. Sometimes, a paracentesis/thoracocentesis is done to determine the presence of malignant cells on cytology, and this is commonly done in our centre. However, only 20% of women will be diagnosed this way. [7] Use of image-guided biopsy of the ovary itself even in advanced cases is largely discouraged due to upstaging the tumour except where the patient is not a candidate for surgery and there's no evidence of disease elsewhere. [8] If biopsy is not feasible, ascitic or pleural fluid aspiration, cystoscopy, and CA-125: CEA ratio of > 25 can be used for diagnosis. [9] Some radio-oncologists in our centre commence neo-adjuvant chemotherapy based on highly suspicious findings on

CT, ascites/pleural effusion suspicious for malignancy and markedly elevated CA-125 levels when a biopsy is not feasible, and patient not fit for primary debulking.

Following diagnosis of ovarian (fallopian tube or peritoneal) cancer, all women should have genetic testing for Lynch syndromes, germline, or somatic mutations for BRCA1 and 2 if epithelial [2] and test for DNA mismatch repair deficiency if clear cell, mucinous, or endometrioid. [10]

Over 90% of ovarian cancers are epithelial in origin, with over 70% of these being high-grade serous with most presenting at stages III (51%) or IV (29%). [11] Other subtypes are clear cell (6%), endometrioid (10%), low-grade serous (less than 5%), and mucinous (6%). [11] High-grade serous ovarian carcinomas (HGSOC) typically have TP53 (up to 90% of cases) [12] and BRCA mutations (up to 20% have germline mutations). [13] They also express WT-1, estrogen receptor, and PAX-8 while low-grade serous ovarian carcinomas (LGSOC) carry BRAF and KRAS mutations. [10]

Even though there is increasing evidence of a common pathogenesis of HGSOC, fallopian tubal, and peritoneal cancer, with similar management modalities, gynaecologic oncologists still advise designating a primary site at surgical-pathologic staging. This is however not routinely done in our centre as immunohistochemistry is not routine.

Our setting largely follows the above protocol to diagnosis except that image-guided biopsies for omental cake or peritoneal carcinomatosis are rarely done and hardly successful, germline and somatic testing are not done, and immunohistochemistry is not routine. For certain reasons, most patients still do not get a histologic diagnosis.

This study therefore aims at determining the proportion of women who present with suspected ovarian cancer that eventually do not get a confirmatory diagnosis and go ahead to discover the reasons for such non-diagnosis.

Materials and Methods

Study Setting – The study was carried out at the Ahmadu Bello University Teaching Hospital (ABUTH), Zaria, located in Giwa Local Government area of Kaduna state, northwestern Nigeria. The hospital was designated as one of the Oncology Centres for Excellence in Nigeria in 2015, alongside five others. It is a centre that provides, screening, diagnosis, treatment, and palliative care for cancers, in addition to training and research.

Our institution therefore serves as a cancer referral centre for other parts of northwestern Nigeria and even beyond. There is a four-year-old Gynaecologic cancer multidisciplinary team tumour board established in May 2019 consisting of Gynaecologists, Radiologists, Radio-oncologists, General Surgeons, Urologists, Pathologists, and Palliative Care nurses. This has gone a long way to improve Gynaecologic cancer care in ABUTH. As with other centres in Nigeria, funding for cancer care is mainly out of pocket, and with 6% [14] or at best less than 10% [15] of the Nigeria population having access to the National Health Insurance Authority (NHIA) funding which is currently compulsory for all citizens and residents. In addition, ABUTH is also one of the centres benefitting from the recently introduced Chemotherapy Access Partnership (CAP) and the Cancer Health Fund which currently doesn't fund ovarian cancers.

Study Design – A retrospective review of all cases of ovarian tumours seen over a 3-year period between 1st September 2016 to 31st August 2019 was done.

Data Collection – All cases that are confirmed, or "highly suspicious," for ovarian cancer presenting to the Gynaecologic Emergency, Gynaecology clinic, and Gynaecology ward of the Ahmadu Bello University Teaching Hospital were included in the study. Case notes, ward admission register, clinic attendance register, theatre records, and histopathology registers were reviewed. Cases histologically confirmed elsewhere but referred to the radio-oncologists for chemotherapy were excluded. Cases of ovarian tumours presenting to the paediatric unit were also excluded.

For the purpose of this study, "highly suspicious" was defined by an ovarian mass > 6cm with any two of the following criteria: malignant radiologic features (solid components, septations, colour in the solid component, presence of ascites and peritoneal masses), pleural effusion, cachexia, anaemia, or evidence of liver metastasis. In addition, malignant cells on cytologic assessment of pleural fluid or ascites also fell into this category.

Complete cytoreduction/complete debulking was defined as the removal of the uterus, cervix, both tubes, both ovaries, omentum, and all grossly abnormal tissues in the abdomen and pelvis at surgery.

An in-depth interview to discuss the challenges each specialty had in the management of ovarian tumours was also done at the gynaecologic oncology multidisciplinary team meeting held on 5th August 2019

Data Analysis – Data was analyzed using Microsoft Excel

Ethical Considerations – This study was part of a larger retrospective review of Gynaecologic cancers currently ongoing at ABUTH. Ethical clearance was obtained from the ABUTH Health Research Ethics Committee (ABUTH/HREC/M3/2019).

Results

A total of 122 highly suspicious cases of ovarian cancer were seen in 3 years. Their mean age was 40.6 years.

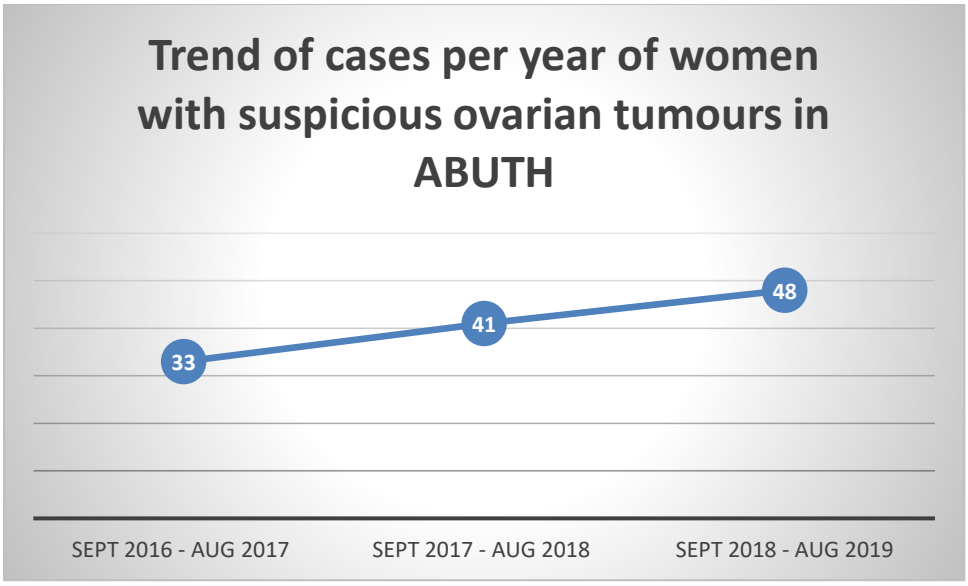

Figure 1: Trends of suspected ovarian cancer cases in ABUTH

Table 1: Socio-demographic characteristics of women with ovarian tumours in ABUTH n=122

Variable	Category	Frequency	Percent
Age	10-25	5	4.1
	26-40	48	39.3
	41-55	36	29.5
	56-70	13	10.7
	71-85	20	16.4
Parity	<2	33	27.0
	2-4	45	36.9
	>/- 5	44	36.1
Level of education	No formal	31	25.4
	Primary	19	15.6
	Secondary	36	29.5
	Tertiary	18	14.8
	Not stated	18	14.8

The majority (68.8%) of suspected ovarian tumours were seen in women between the ages of 26-55 years.

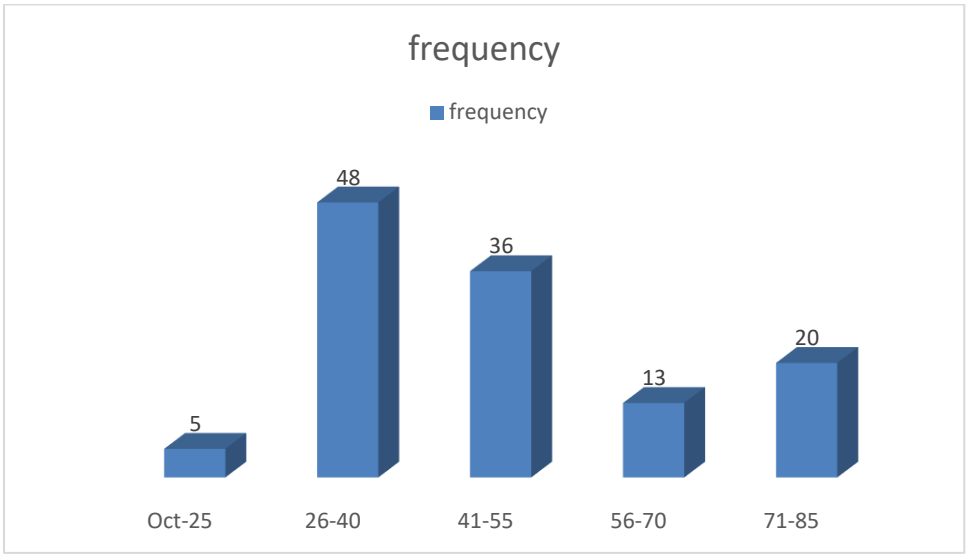

Figure 2: Bar chart of cases by age of ovarian tumours in ABUTH

Solid components with colour flow on the doppler were seen in 62%. Ascites (either clinical or radiologic) were the most common feature present in 88% of cases, while anaemia and cachexia were seen in 23% each. Other features such as pleural effusion was seen in 5.2%, while 4.9% had liver metastasis on ultrasound and/or liver function test derangement. The majority (63%) were multiparous.

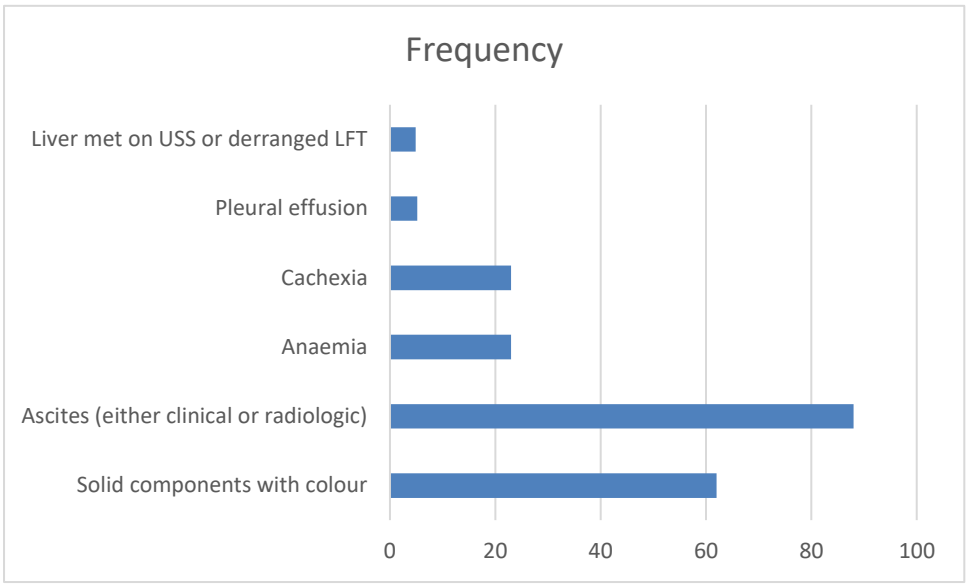

Figure 3: Findings suspicious of ovarian tumours in ABUTH

Twenty-three percent of suspected ovarian cancer cases (28/122) had surgery. Of these,13 (46.4%) upfront and 15 (53.6%) interval debulking surgery (IDS) following neoadjuvant chemotherapy (NACT) based on malignant cells on cytology or CT scan findings and elevated tumour markers.

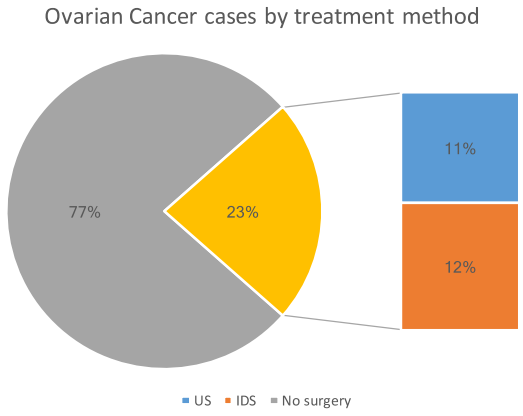

Figure 4: Ovarian cancer cases by treatment method

The majority i.e., 94/122 (77.1%) had no surgery or biopsy and hence had no histological diagnosis. There were documented attempts at image (ultrasound) guided biopsy in 3 patients, but they were not successful. As high as 37.2 % of patients who didn't have surgery (35/94) were lost to follow up before a definitive plan could be carried out.

Only two cases out of the 28 that had surgery had documented complete (R_0) debulking/cytoreduction (7.1%) which is the removal of visible disease from the abdomen. Other patients had no documentation of the extent of resection in their operation notes or case folders.

Among those that had upfront surgery, one case (7.7%) was an ovarian fibroid and two (15.4%) were borderline tumours. The remaining 10 cases were malignant (76.9%). All patients that had secondary cytoreductive surgery/interval debulking surgery (IDS) following 3-4 cycles of chemotherapy had malignant histology. Hence 25/28 (89.3%) of patients who had surgery for highly suspicious ovarian tumours had ovarian cancer confirmed. The distribution of the 25 ovarian cancers is shown in Figure 5.

Table 2: Histotypes of Ovarian Cancer as seen at ABUTH.

Variable	Category	Frequency
Epithelial	HGSOC LGSOC Mucinous	8 1 3
Sex Cord	Granulosa cell Fibrosarcoma	7 1
Germ cell	Dysgerminoma	2
Metastatic	Metastatic	3

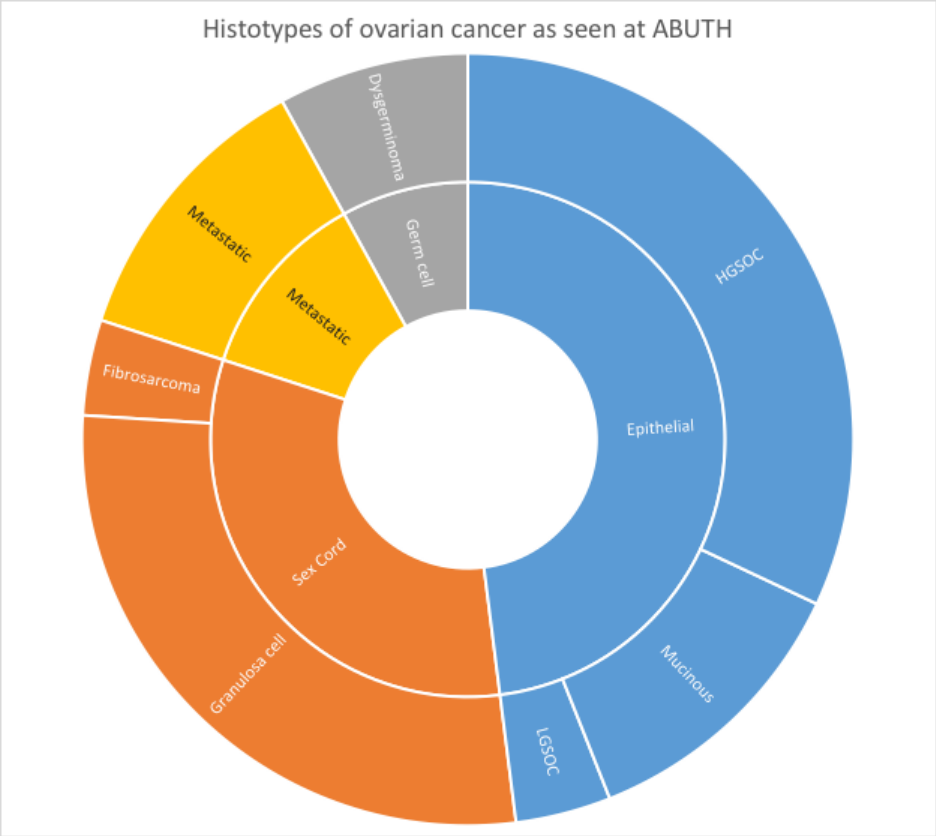

Figure 5: Histotypes of ovarian cancer cases as seen at ABUTH.

Management challenges as summarized from the in-depth interview include:

General (mentioned by every specialty) – Late presentation of cases hence may be unfit for surgery or chemotherapy, insufficient funds for treatment with poor coverage of health insurance for cancer care.

Gynaecologic oncology - Inadequate skills of some health care providers. No formal gynae-oncology training in Nigeria. Lack of enabling environment to practice acquired skills. Poor record keeping as much difficulty was experienced retrieving records from torn and damaged books.

Radiation/clinical oncology – no formal medical oncology training program in Nigeria. Poly Adenosine diphosphate Ribose Polymerase (PARP) inhibitors are not available. Bevacizumab, a vascular endothelial growth factor inhibitor that acts as a targeted therapy for most ovarian cancers, is generally not affordable. Non-availability or prohibitive cost of some chemotherapeutic agents. Few drugs are currently available on the CAP, Inadequate capacity to manage toxicity.

Radiologic - Non-functional computerized tomography scans. The two-slice CT was broken down at the time of this interview and patients had to get their CT scans from the Kaduna metropolis (about 80km distance) at a higher rate. Unavailability of positron emission tomography (PET), lack of interventional radiology facility amongst others

Pathology - Unavailability of routine immunohistochemistry. No Germline and somatic testing. Inadequate cytopathologists, lack of frozen section

Discussion

According to the National Cancer Institute's Surveillance, Epidemiology, and End Results program data, the incidence of ovarian cancer is declining globally, accounting for 2.5% of all new global cancer cases in 2018.[16] This trend was however, not demonstrated in our institution where Zayyan et al previously demonstrated that the number of cases of ovarian cancer increased over a ten-year period [17] and the current study corroborated this. A similar study in another part of Nigeria has also shown a rising frequency. [18] The reason for this rise may be related to the increase in awareness and health-seeking attitude of the women in this region, as well as subtle advances in the management of ovarian cancer in the region. Other proposed factors include population growth, increased cancer risk factors, decreased pregnancy, and lactation length as well a decrease in tubal ligations. [19]

Ovarian cancer is generally a disease of older women. About half of the women diagnosed are 63 years or older. [20] The incidence rises steeply after the fifth decade to reach a peak in the 80- to 84-year-old age group. [21] In this study, however, the mean age of cases was 40.6 years. This is in keeping with a previous study in this institution by Zayyan et al where greater than 50% of patients were young women less than 40 years. [11] Studies in other parts of Nigeria and the African region and black women in the diaspora agree with this finding. [22] In comparison to White women in the United States, women of African ancestry have a lower incidence of ovarian cancer. [17] However, Black women have higher morbidity and mortality rates, higher unstaged and unclassified tumors, and are thus undertreated or untreated with subsequent compromise in progression-free survival. [23] Data also suggest there are health disparities across the entire cancer continuum from prevention to treatment, but few studies exist to directly address these disparities.

In this study, the majority (63%) were multiparous. This was also demonstrated in the previous study in our institution. [17]

No matter how high the index of clinical suspicion, the diagnosis of cancer is not conclusively established nor safely assumed in the absence of a tissue diagnosis. [18] An accurate, specific, and sufficiently comprehensive diagnosis is required to enable the clinician to develop an optimal plan of treatment and invariably estimate prognosis. [24] The majority (77%) of the 122 cases reviewed had no histological diagnosis. Reasons for this include the known difficulty with obtaining tissue diagnosis in ovarian cancers (as ovaries are deeply situated in the abdomen), non-availability of interventional radiology for image-guided biopsy, the reluctance of the gynaecologists to take patients for upfront surgery due to poor performance status or uncertainty of disease extent, the inability of radiologists to tell with certainty the extent of disease on imaging or more frustratingly, the inability of the patients to pay for surgery. This means that the statistic for ovarian cancer is probably under-reported as compared with other cancers such as cervical cancer; where the histological diagnosis is much easier and cheaper as it doesn't involve surgery in my centre, with cervical biopsies done in the clinic, ward, or emergency unit at first presentation. In addition, the GLOBOCAN statistics were extrapolated from registries outside the 19 northern states of Nigeria. The Abuja registry, located in the cosmopolitan Federal Capital Territory Abuja, might not be truly representative of the north.

There is a high percentage (52%) of non-epithelial tumors from this study. This contrasts with studies among the Caucasian population but in keeping with findings from other African studies [17,22,25,26]

Some challenges identified by the MDT include poverty and poor coverage of health insurance for cancer care making patients unable to pay for investigations. According to the World Poverty Clock, Nigeria has the most extremely poor people in the world, with almost half the population living on less than $2 per day. [27] The majority of our patients cannot afford investigations to confirm diagnosis making surgery and chemotherapy a mirage. It was not until October 2019, that the Federal Ministry of Health, in partnership with the Clinton Health Access Initiative (CHAI), the American Cancer Society (ACS), Pfizer, Worldwide Health Care, and EMGE Resources, launched a pioneer Chemotherapy Access treatment program called chemotherapy access Partnership (CAP), to cater for 50% of treatment cost in people with cancer. [28] This will enable patients to access high-quality chemotherapy agents (same as those used in the United States) at seven teaching hospital pharmacies in Nigeria including our centre, ABUTH. All these problems might result in the remaining 77% of patients dying without a histologic diagnosis.

Loss to follow up before a definitive diagnosis, which may be finance-induced or as a result of inadequate counseling with denial or cultural and religious beliefs that cancers are not treatable in the hospital, was common in this study (37%). In addition, the general belief that cancer is a terminal disease probably reduces individual and philanthropic funding for cancer patients. It is also a known fact that there is inadequate manpower in the health facilities to efficiently cater to the needs of patients generally and cancer patients specifically due to the massive brain drain in Nigeria. [29] The results of the ongoing Every Woman Study: Low- and Middle-Income Countries edition [30] will provide more insights into these challenges.

In addition to these, adequate facilities and technology for cancer management are lacking. There are only a few functional cancer centers in the country (none in the 19 northern states as of January 2023) to cater to the needs of the 233,911 cancer patients in the country. [1] Only 20-25% of ovarian cancers are diagnosed early in stage I/II, [11] because of late presentation due to aforementioned reasons. This also plays a part in the late diagnosis. Staging of ovarian tumours is surgical-pathologic and as such a patient cannot be fully staged if she doesn't have some surgical intervention.

Some patients die from complications of the late disease such as severe anaemia, respiratory failure, thromboembolic events et cetera with which they present. Aside from these probable explanations, an in-depth study will need to be carried out to determine the root cause of failure to make a histological diagnosis in patients with suspicion of ovarian cancer.

Findings from this study indicate that the likelihood that ovarian cancers are being underestimated is high due to difficulty in getting a histologic diagnosis which involves surgical intervention or interventional radiology. The late presentation of patients and poor performance status may make them unfit for surgery while interventional radiology is unavailable.

In addition, the role of prevention in ovarian cancer cannot be over-emphasized. It is pertinent, particularly in this region recording a rise in ovarian cancer cases, to research, implement and familiarize gynaecologists with recent advances in screening for early ovarian cancer. This is important in women with established risk factors for the condition such as a family history of ovarian cancer, and Lynch syndrome. Risk scoring using the Risk of Malignancy Index (RMI), Risk of Ovarian Cancer Algorithm (ROCA) as well as other risk algorithms can be applied to estimate the risk of malignancy thereby triaging patients before definitive staging or histological diagnosis. The ideal screening test for ovarian cancer has remained elusive. The most investigated biomarker for ovarian cancer is serum CA-125 and although studies remain inconclusive, it has been recommended for screening of high-risk women alone or in combination with other parameters such as transvaginal sonography, pelvic examination, et cetera. [31,32] Furthermore, elective or prophylactic (risk-reducing) bilateral salpingo-oophorectomy has been proven to reduce the risk of ovarian cancer in women, particularly those of average and high genetic risk. [33] Opportunistic bilateral salpingectomy with ovarian retention (BSOR) has also been postulated to decrease both the incidence of and mortality from ovarian cancer while retaining normal ovarian function and thus, quality of life. [31] This is currently being performed in our centre. Tubal ligation is also thought to decrease the risk of ovarian cancer; the mechanism via which it does this is not well understood. It has however been consistently found to provide a 50% reduction in epithelial ovarian cancer risk. [33]

In view of the minimal attention paid historically to cancer in Africa, the number of cancer specialists as a proportion of all healthcare workers is probably low. [34] Additionally, inadequate resources for pathology lead to an inadequate workforce, poor facilities and equipment, and low availability of immunohistochemistry. [35]

Conclusion

Most patients with features highly suspicious of ovarian cancers didn't have a tissue diagnosis, hence probably dying undiagnosed. Management of ovarian cancer in our setting remains a challenge despite advances in surgical and chemotherapeutic options. Infrastructural development, prompt tissue diagnosis using interventional radiology or laparoscopy for biopsy, and training of all disciplines involved is recommended.

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