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RESEARCH ARTICLE

CHALLENGES AND OPPORTUNITIES IN CANCER DIAGNOSIS IN ETHIOPIA: IN-DEPTH EXPLORATION OF PRACTITIONERS' VIEW

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ABSTRACT

Background: Despite all its critical roles in cancer detection, directing therapeutic approaches and patient management, the state of pathology service in Ethiopia and factors affecting its role are not documented.
Objective: This study intends to explore the challenges and opportunities of cancer diagnosis in Ethiopia.
Methods: The study was conducted at the Black Lion Specialized Hospital (BLSH), Addis Ababa, Ethiopia. Purposive sampling technique was used to identify pathologists to participate in the study. A qualitative method using semi-structured interview guide question was employed to address the problem. A total of 16 pathologists were involved in the study. Interview was audio-taped following permission secured from each participant. Data was analyzed using thematic analysis.
Result: The finding of the study shows that personal provider level challenges and lack of equipment and supplies affect pathology service provision at BLSH. Negative attitude of patients towards diagnostic procedure, inadequate training of the professionals, shortage of skilled human power are personal level challenges affecting pathology service provision. On the other hand, lack of quality reagents and equipment, poor maintenance efficiency, weak logistic system for delivery of specimens and poor ICT services ware the other major bottle-necks hindering cancer diagnostic services in Ethiopia. The initiative to operationalized tele-pathology was identified as a major opportunity to improve cancer diagnostic services.
Conclusion: Improvement of the pathology service requires all stakeholders (the experts, authorities, and the community) to work together to up-lift the pathology service from its sub-standardized status in Ethiopia. The department has to be dedicated to look the opportunities through the challenges-by developing SOPs, digital documentation and initiating sub-specialty programs.

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INTRODUCTION

Despite huge investments and continued investigations, cancer remains one of the critical areas of public health concern in the world. Every year almost 7 million people die of cancer worldwide and nearly 75% of cancer-related deaths occur in low and middle income countries (LMICs). Such cancer caused death is projected to increase from 7.9 million in 2007 to 11.5 million in 2030 and three-fourth of these is expected to be from LMICs (Bray, 2008; Torre, 2015; Beaulieu, 2009 and Ferlay, 2010). This dramatic increment in mortality rate is partly attributed to an increasing and aging global population and fast spreading sedentary life in the LMICs (Baan, 2007; Key, 2002; Vainio, 2002; Jemal *et al*., 2010). In the West, personalized therapy has benefited from precision medicine and more particularly from advances in pathology services that

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applies modern diagnostic molecular technologies (Porter, 2008). Coupled with introduction of screenings and vaccinations, such personalized therapy has contributed to the reduction in cancer mortality rate in high income countries (Jemal, 2010). Generally, most cancers are detected at advanced stage of the disease, where the patient can not benefit from the potential treatment approaches. This is particularly true in LMICs, where there are very poor awareness of the people about cancer (Porter, 2008; Richards, 1999; Lyratzopoulos, 2015). In addition, access to advanced cancer diagnostic centers (pathology laboratories) is limited in many LMICs. Pathology examination, being a gold standard method to diagnose cancer, is crucial for accurate determination of cancer morbidity and mortality. It also plays pivotal role in initiating appropriate treatment, monitoring the therapeutic responses and forecasting the prognosis of cancer patients. Pathology diagnosis is also a vital precondition for establishing national and regional cancer registry centers. Without well-established diagnostic pathology center it is impossible to try to control and treat cancer in any state. Despite such realities, pathology service together with the manpower in the field is extremely abandoned in Africa, particularly in sub Saharan countries, including Ethiopia (Adeyi, 2011; Benediktsson, 2007; Petti, 2006 and Awadelkarim, 2010).

More regretfully, pathologists in the region are extremely disappointed in the exiting pathology diagnostic set ups, the procurement systems, awareness of people about the service and lack of attention by the authorities (Petti, 2006). These are one of the reasons why most of the pathologists from Sub Saharan Africa are forced to dislocate to Western countries to practice their profession effectively (Mills, 2011 and Hagopian, 2005). In Ethiopia, pathology service was established in 1965. Since then, the demand for pathological examination by patients and/or caretakers has increased with commensurate rise in morbidity of cancer at BLSH. The routine operations of pathologists at BLSH are influenced by several factors. The objective of this study was to explore the challenges and opportunities facing cancer diagnosis in Ethiopia. Evidence generated through this study is expected to be used for strategic and programmatic response.

MATERIALS AND METHODS

The study was conducted at Black Lion Specialized Hospital (BLSH), Addis Ababa, Ethiopia. The hospital is a tertiary level teaching hospital under the college of health sciences of Addis Ababa University. It offers diagnosis and treatment services for approximately 370,000- 400,000 patients in a year. There are 16 regular outpatient departments (OPD) providing services to new and repeat patients. Some of the chronic cases' follow up are not done on a daily basis due to an over-crowd of the departments. Pathology department in BLSH is overwhelmed with the workload and old laboratory establishment that has not been renovated (Fig 1). Yet, the department gets samples from gynecology department, surgery department, internal medicine department, dermatology department and other hospitals within the city and periphery since it was been the only pathology center for cancer diagnosis in the country. Annually, 8000 biopsy and 2000 FNA specimens are diagnosed in pathology department. Qualitative descriptive study design was employed. Purposive sampling technique was applied to select the study participants. A semi-structured interview guide was developed in line with the objective of the study. Interview was audio-taped following permission from participants. The interview topics covered challenges, solutions attempted, opportunities and strategies to improve cancer diagnosis in the department. The interview topics were reviewed by experts in the field and pretested before it was applied for the actual study. Participants were experienced pathologists and senior residents who were working at BLSH for an average of 16 years (range 2-30 years). There were a total of 8 pathologists out of which 2 were on annual leave at the time of data collection and excluded from the study. The remaining six staff members were selected for interview. Moreover, there were a total of 17 pathology residents of which 10 were at the department for at least two years. All of these were involved in the study. After a brief introduction about the purposes of the study as well as the confidentiality of the information collected from the respondents, verbal consent was obtained from participants. Primary investigator with support by one research assistant did the interviews.

Fig 1. Pathology laboratory partial view. This is the microscope room where seniors and residents look slides under microscope. This room might have not been repaired for decades

Interview was conducted using interview guides at BLSH where participants feel at ease to discuss with data collectors. Interviews were audio-taped with permission from every participant. Each interview took an average of 45 minutes. Data was transcribed and read by two independent coders helped to define themes in reference to the objectives. Variations between the independent coders were discussed to reach at common themes. Accordingly, patient related challenges, facility related challenges, health care provider related challenges, technology related challenges, and opportunities in cancer diagnosis were identified as major themes. Raw data was categorized under these major themes. Thematic analysis was employed to analyze and interpret results.

RESULTS

A total of 16 pathology professionals at BLSH were interviewed on challenges and opportunities of cancer diagnosis. Out of these 6 were senior faculties in the department while the rest were second year and above residents that have been specializing in pathology. The composition of respondents shows that 75% are male while the remaining proportion is female as indicated in Figure2.

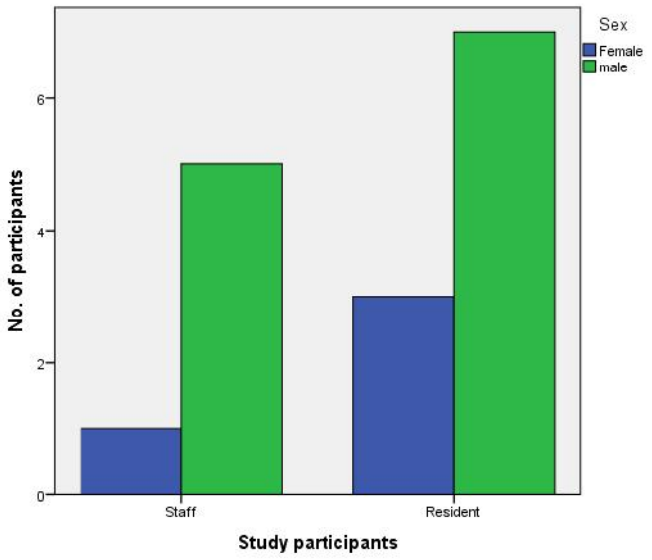

Figure 2. Composition of study participants

Work history of respondents shows that participants worked at the department on average for 16 years which ranges from 2-30. Of the six experienced pathologists, five were general pathologists while one was a subspecialist in cardiopathology (expatriate cardiopathologist). The respondents were only from Black lion Specialized Hospital as it has been the only experienced public cancer diagnostic and treatment center so far. Details of the findings are presented under the five themes: patient related challenges, facility related challenges, health care provider related challenges, technology related challenges, and opportunities in cancer diagnosis.

Patient related challenges

Language was one of the major challenges in pathology service provision at BLSH. Patients come from all parts of the country and often they do not speak the working language. As a result, practitioners require translator to properly understand the client's problem. In view of the fact that providers are stretched to meet the demands of patients waiting for their turn, looking for translator in such situation wastes. Since all cancer patients are referred to BLSH, the hospital is always congested with large number of patients seen every day and many more are still waiting for their turn. Coming from all corners of the country and at times having no relative to stay with, patients found it difficult to bear the cost of stay in the capital city. Almost all the patients were said to come to the hospital at the late stage of the disease [stage III or IV]. One of the respondents replied,

"...Majority of patients come at stage III and IV. They preferred to stay at home rather than going to hospital, hoping that they may get relief from the disease spontaneously. Some come after attempting traditional means and this can be taken as one reason for their presentation at the late stage of the disease..." [PI-1].

It was found that patients have respect to physicians and comply with instructions from practitioners. However, there were times when patients tend to resist chemotherapy or surgery. Such patients intend to try traditional healing. One of the respondents pointed out that

"...A number of patients preferred to go to church or mosque as they perceived that the cause for cancer is transgression of God's law or devil spirit, miscarrying proper rituals. …they wanted to go to traditional healers since traditional medicine gave them immediate but temporary symptomatic pain relief from the disease...patients resist chemo or surgery because of the side effects that come following the treatment. Moreover, they believe that spiritual solutions are more effective than chemo and surgical therapy." [PI-2]

The practitioners reported that their patients were not happy with the cancer diagnosis procedure. Among others unhappiness with the diagnosis procedure has to do with the extended time it takes to know treatment options and waiting time for receiving result. It was also found that study participants are frustrated with the time spent in the peripheral hospital. Having come selling their property to get cure from cancer, waiting longer to know their health status discomforts the patients and so is the case for the providers. One of the participants reiterated that

"… Some patients come from periphery and are very poor to afford accommodation and medical expenses. In addition, the waiting list is very long. They were forced to stay some time for about 15 days for biopsy and three days for FNA before they know the result. This exposed the patients for extra expenses. As a result, they are not happy about the diagnostic procedure… but we now have planned to issue the result within a short period of time (within one week)"[PI-5].

Provider related challenges

Study participants were found to have diverse training on special pathological techniques such as immunohistochemistry (IHC), flow cytometry and fine needle biopsy aspiration [FNBA]. In addition to training, it was gathered that, senior pathologists and residents meet twice a week during slide sessions and journal clubs to discuss on complex cases and share new scientific developments on cancer diagnosis. Besides, through IPath-inter pathologists' observation program

between pathologists of BLSH and pathologists elsewhere in the world such as UK, USA, and Israel and participation in the online conference with pathology department in the University of Basel (Switzerland), provider's knowledge and skill has been continuously updated. Despite such trainings and strong feeling of professional skill in specific techniques, such services were provided on fragmented fashion mainly due to lack of sustained availability of reagents. Another big challenge mentioned by study participants was confusing results of specimens. It was reported that tissue specimen were sent to different pathologists to generate individual opinion to have consensus in reporting results. Patients get confused when they hear different diagnostic results. One should not be wondered with the discrepancy in diagnostic result as cancer diagnosis in BLSH pathology department solely relied on morphology, which is unspecific and inaccurate to certain degree. In addition, the clinicians do not report patients' clinical history to the pathology department. Moreover, patients do not tend to tell their clinical history. This has serious impact on final decision of the result, particularly, in case of patients who had been diagnosed for cancer and who were under treatment for certain period of time but interrupted the treatment at some point in the past and come again for diagnosis. It was found that study participants are not financially stable that they have to raise money on a part time basis. As a result they do not dedicate their full time to service provision and research activity.

"We have received trainings by inviting visiting professors from North America, Canada and Europe. There is also a possibility of participating in international academic pathology conference but there is no ear-marked budget for this. It is highly relied on the commitment of the professional. We have online conference with the Basel University" [PI-4].

Facility Related Challenges

Respondents estimated that there were around 9000 [more than 2000 clients] pathology specimens examined in the laboratory per year, an estimated 90 specimens a day. At the hospital, cancer is diagnosed primarily using anatomical pathology/morphological techniques. However, the study participants stated that morphological diagnosis can correctly diagnose tumors in 90-95 percent of the cases if properly processed. Immunohistochemistry is a differential diagnosis to investigate the origin of cells and it has great potential to indicate appropriate therapeutic approaches. Nevertheless, participants reported that immunohistochemistry service was not rendered in sustainable manner at the hospital. They said that the IHC service in pathology department has fragmented nature. The service was introduced in 2006 with support of British council. Since then it has been mostly provided by personal commitment of one expatriate pathologist who used to buy antibodies from his personal pocket and/or raise support through his personal contact. One of the respondents emphasized that:

"...Immunohistochemistry service is not available. Even I wonder if people know the importance of immunohistochemistry. This is very disappointing and discouraging for a specialized hospital. We cannot claim to help patient without such specific diagnostic test! This frustrates and makes us helpless. Given the current rise in the incidence and prevalence of cancer in Ethiopia, lack of such useful diagnostic tool is no less than social murder [PI-4].

The other main challenge was sample handling skill of the concerned professionals, mistakes in sample transport and unrepresentative sample. They reported that samples were poor in quality or unrepresentative. Moreover, the samples were sent without fixative [formalin]. Thus, the patient sample is deteriorated by the time it arrives in pathology department. This will lead the pathologist to wrong diagnostic decision and it ends up with wrong treatment, consequently, the pathologist loses trust. In addition, the specimen senders from peripheral hospitals do not send with full information about the client such as the age, sex, x-ray findings and clinical information. These have great value on the interpretation of the pathology results. Lack of clear cross-talk with oncology department was another challenge reported by the study participants. There is no forum that brings the two departments together. One of the respondents remarked:

"...No history of the patients is available. We do not know whether the patient is on treatment, interrupted the treatment and come back for second diagnosis or newly admitted. Consequently, patients would say that last time the diagnosis was this but now you said the diagnosis result is different and they ask which one is correct. This leads to patient confusion and as a result our work will be distrusted" [PI-1].

However, the pathology department has good relation with other departments such as gynecology, pediatrics, orthopedics, internal medicine and surgery. According to the respondents, there was clinico-pathologic conference between these departments to exchange clinical information. Poor procurement and logistic system to ensure sustainable availability of reagents and equipment was a major challenge identified by all participants. The reagent and equipment were of poor quality imported for low-cost that readings are blurred for microscopic images. Due to the fact that there are no antibody and reagent suppliers in the country, the service has been impaired for long period of time. At times it was reported that the department interrupted service delivery for weeks due to lack of absolute alcohol, xylene, or any other simple chemicals in the department. This was attributed to poor logistic management. There was shortage of equipment and reagents like microscope with inbuilt camera for digital imaging and image analysis. All of the respondents explained about the problem of supply chain and procurement as follows:
"...We have several concerns. Sometimes formalin, xylene and other reagents are unavailable for about one or two months. Tissue processor and other equipment were not maintained in time. In addition, there was severe shortage of microscopes with in-built digital camera to take the slide images" [PI-4, PI-5]

Technology related challenges

The fragmented ICT service was reported to be one of the challenges for ongoing pathology education and histopathology laboratory services. Moreover, lack of well-trained data manager and reliable data management system resulted in frequent loss of patient results. One of the respondents explained that:
"...ICT service is almost non-existent in the department, as a result diagnosis reports are written by the conventional secretary. Consequently, typing error is common since the secretary is not familiar with the medical words and terms. As a result, the pathologist has to waste plenty of time in editing

typing errors in result report. There is no continuous internet service [PI-5].

Opportunities

As the main academic and referral center in the country, BLSH has major opportunities to serve as a hub for rapid development of pathology in Ethiopia. The pathology department is the first one with residency program producing trained pathologists for the peripheral hospitals. As such, the department is responsible to take steps to improve pathology services in the country. The recent initiative to launch telemedicine is expected to play important role to advance teaching, research and service provision on cancer. It also facilitates timely diagnosis and communication of result. Moreover, there are several ongoing trainings on up-to-date pathological techniques in collaboration with international Universities. The demand for pathology residency is also extremely increased, strengthening the shoulder of the department to withstand ever increasing burden of cancer diagnosis in the hospital.

DISCUSSION

Pathologic diagnosis is a gold standard to diagnose cancer and it plays pivotal role in the detection, treatment and monitoring of cancer (Petti, 2006 and Awadelkarim, 2010). Particularly, histopathologic examination is the main source of information on tumor characteristics and directs selection for appropriate therapeutic approaches by clinicians. It also plays important role in the development of bio-banks which is a corner-stone for translational research in clinical sciences. Good oncological practice and appropriate treatment approaches for cancer is possible only if standard pathology service is available in a hospital (Awadelkarim, 2010). Despite all its useful aspects, pathology service in Ethiopia was found to be compromised by challenges. In this study, factors that affect pathology service were categorized into patient, provider, facility and technology related challenges. As is evident from the finding of patient related factors, language was found to be one of the barriers. This can surely happen in a country in which more than 80 languages are spoken. In a country with over 80 different languages, it is not surprising to identify language as a barrier. Pathologists spent much of their time looking for somebody who can interpret the language of the patients. This consumes much time and results perhaps in unnecessary delay of the result report. This is not unique to pathology service since it is commonly observed for other forms of medical services elsewhere in the world and resulted in compromised health care service provision (Scheppers, 2006). Another study indicated that language barrier is one of the crucial factors to impair the benefit of patients from medical service where medical interpreter services are recognized as critically important for quality health care service provision (Flores, 2005 and Okrainec, 2015). Black Lion Specialized Hospital is always and all the time crowded with patients and attendants who come from different corners of the country. Most of patients come from rural areas where the working language is poorly spoken. As it is the only public national cancer referral hospital any other hospitals either from periphery or in city refer to Black Lion Specialized Hospital when the case is beyond their capacity and not promising. Thus, the hospital is overloaded with complicated cases, some of which are at their last stage and need serious palliative cares, which is completely lacking in this hospital. The later problem, taken together with the language barrier, indicates that the BLSH needs medical interpreter not only for pathology department but also for other departments to provide at least, satisfactory clinical services. The attitudes of patients about cancer diagnosis have also significant impact on pathology services. Some consider that cancer is incurable curs from God. Thus, they prefer to go to religious places and or traditional healers. There, they spend most of their time and come to diagnostic centers after the disease has escaped beyond it can be reversed (Biswas, 2014). In general, patients do not like to come to pathology diagnostic center due to the prolonged turnaround time of the pathology results and serious side effects of chemotherapy and radiotherapy. Usually, the society has bad experiences about cancer in this country because it is most unlikely that one survives from cancer. This is because the patients are presented at advanced stage of the disease and there is poor facility for early detection and accurate treatment. Furthermore, patients who come from rural part of the country do not afford for accommodation, living expenses and transportation in Addis Ababa. In addition, some patients spend significant time in peripheral hospitals before they are referred to pathology department in BLSH. Then, when they get diagnosed for cancer in BLSH, the tumor has already spread and treatment will not have the potential to cure or prolong the survival of patients. These are common complex challenges observed also in every corner of low and middle income countries and have to be addressed by public health educators in these countries carefully (Petti, 2006; Awadelkarim, 2010; Biswas, 2014; Birhanu, 2012).

The current study also indicated that patients gave priority for traditional and spiritual means for their cure from cancer. Once they were told that they had cancer they panic and did not want to take modern medicine before attempting the traditional ones. These results are in agreement with the findings of a similar study done in Kenya where cervical cancer screening was viewed negatively by clients and some health care professionals (Kivuti-Bitok, 2013). Despite the limited number of experts, the pathology department at BLSH has well-trained senior pathologists. Of course, the department has shortage of experts who has sub-specialized in different specialty areas. This is not unique to BLSH rather it is the common shortcomings of other Sub Saharan African Hospitals (Petti, 2006 and Awadelkarim, 2010). To fill this gap, some of the up-to-date pathological techniques are acquired through trainings that were facilitated by the Addis Ababa University in collaboration with foreign Universities. In addition to making life easy for treating clinicians, this kind of trainings are very important to accurately diagnose cancer and increase the chance of cure for the patient. However, most of the trainings are not applicable for routine diagnostic services. This is partly because the acquired techniques need very expensive kits and reagents in addition to high-tech trained technical operators. That is why the pathologists rely only on morphological diagnostic means, mainly hematoxylin and eosin staining. Lack of immunohistochemistry was continued to be the main bottleneck of the department as some tumors are completely undifferentiated with the conventional pathological techniques. The effect of this problem was not limited to compromising the diagnostic service but also on professional commitment and job satisfaction, which were manifested by the overt signs of frustration and hopelessness in the experts. This made the practitioners not to feel that they are properly helping the patient. This is in line with the study of Patel and his colleagues (Patel, 2016). They showed experimentally the

importance of development of affordable immunohistochemistry services for cancer care in low and middle-income countries. However, it is noteworthy to mention that some of the flow cytometry and immunohistochemistry are also applied intermittently. This is because the hospital bill is extremely cheap, even mostly provides free service, as a result it cannot recycle the money expended to carry out this diagnosis. This indicates that revising the medical bills and including the important up-to-date diagnostic techniques in every day routine activities is urgently needed. Clear intercommunication among the clients and the service provider is very important. Patients have to inform the pathologist everything about their clinical information. The pathologists in BLSH do not have any contentious relationship among themselves. But it is essential to have clear regular communication with other departments. Without purposeful interdisciplinary crosstalk it is impossible to imagine fruitful and accurate diagnostic services, in turn, no effective treatment approach. The ultimate goal of interdepartmental [clinicopathological] communication and or intradepartmental and provider-client communication is to see the patients get cured. The current study revealed that the pathology department in BLSH lacks smooth and clear communication with some important departments like oncology and surgery departments. This could be partly because the clinicians are extremely busy in wandering here and there for generating additional income to support their family and improve their life. However, in any means and by any cost, it is essential to establish a clear and strong communication at least with oncology department in regular basis. This is because lack of good pathologist-oncologist and client-attending clinician communication would result in a serious problem, till losing the life of the patient. This finding is clearly supported by a study from Nigerian hospital, which witnessed that lack of good communication between the clinician and pathologist may make diagnosis difficult or impossible, in turn, hurts the patient (Suleiman, 2015). In addition, it is not only frustrating to stakeholder departments but is also a very dangerous for the patient with potentially enormous medical, legal, and financial consequences. Present study also indicated that there is poor logistic system for transporting specimens.

The specimens are transported by the patient or the attendants. Biopsy samples are either poorly fixed or/and spoiled with dirt, which impairs the normal function of instruments in the diagnostic center. Inadequate training and poorly skilled technicians for tissue processing and sectioning were the main challenges related to health care workers. All of these challenges may aggravate the poor diagnostic service situation in the hospital. This type of weak logistic system, coupled with unclean specimens, is partly responsible for unreliable results and elongation of turnaround time. Similar study indicated that most of the pathology departments and diagnostic laboratories in Africa in general and sub Saharan Africa in particular suffer from lack of laboratory consumables, shortage of basic essential equipment, limited numbers of skilled personnel, lack of educators and training programs, inadequate logistical support, insufficient monitoring of test quality and lack of governmental standards for laboratory testing (Petti, 2006). The involvement of staffs for collective decision making in regular slide discussion sessions could be taken as something that should be strengthened. This is because apart from decreasing errors in diagnosis, it may positively be taken as a good opportunity to strengthen team spirit, team-cohesion and productivity. In addition, the application of telepathology has to be fully implemented. However, the poor ICT service can be taken as an impediment for pathology teaching, training, expert advice and quality control. These findings support a report from Sudan where the pathology service was underdeveloped and characterized by shortage of pathology service, poor quality of reagents and equipments, poor handling and storage of specimens and unfavorable environmental condition for the transport of samples (Awadelkarim, 2010 and Kivuti-Bitok, 2013).

Conclusion and recommendations

We identified the potential bottle-necks that hinder effective cancer diagnostic services provided by pathology department in BLSH, Addis Ababa, Ethiopia. The challenges are versatile and composite of economic, political and socio-cultural features surrounding pathology service in Ethiopia. Consequently, future pathology service development initiatives should confront with these spectra of challenges. The fact that there was poor sampling, handling, transportation and storage of specimens made the service rudimentary. The concerned bodies should be aware that cancer diagnosis is different from the routine laboratories that we have here and there in the health centers and hospitals. Cancer diagnosis needs dedicated pathologists with cutting-edge pathology laboratory. With increasing number of the current population [>90 million], it is regretful to have no a single Ethiopian sub-specialized pathologist in Black Lion Specialized Hospital. Trainings for laboratory technologists and logistic workers are extremely important to improve specimen quality. Public health education is also needed to improve the attitude of people about the modern medicine. In addition to up grading the department in terms of documentation, creating opportunities to young ones to sub-specialize in different pathology fields, the BLSH pathology department has to play a lead role in quality pathology service, beyond the BLSH. Use of non-probability sampling technique and low number of interviewee are the limitations of this study.

List of abbreviations

BLSH-Black Lion Specialized Hospital
ICT-Information and communications technology
LMIC-Low and middle income countries
OPD-outpatient departments
IHC-Immunohistochemistry
HE-Hematoxylin eosin
SOP-Standard Operating Procedure
FNA-fine needle aspiration

Ethics approval and consent to participate

No ethical approval is applicable but pre-informed consent has been accepted from the study participants.

Consent for publication

Our manuscript does not contain data from any individual person. Thus, we state that this section is "Not applicable".

Availability of data and material

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors have declared that no competing interests exist.

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Authors' contributions

- HW: Conceived and designed the study, analyzed the data and participated in acquisition of data and drafting manuscript.
- WLL: Conceived and designed the study and was involved in acquisition of data and writing the manuscript.
- MK: Involved in data analysis and critically reviewed the manuscript.
- TM: Involved in acquisition of data and design of the study.
- MA: Involved in acquisition of data and design of the study.
- All authors read and approved the final manuscript.

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