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Histopathological Study of Carcinoma Cervix through Reviewing of Female Genital Tract Cancer Cases of Pathology Archive, Benghazi University from (2002-2011)

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الملخص

الجهاز التناسلي للأنثى هو موقع من أكثر الأورام شيوعا عند الإناث. والنوع الأكثر شيوعًا من سرطانات الجهاز التناسلي للأنثى هو سرطان عنق الرحم والمبيض وسرطان بطانة الرحم. وهناك أورام أخرى أقل شيوعًا بما في ذلك أورام المهبل والفرج وقناتا فالوب. إنّ سرطان عنق الرحم هو ثاني أكثر أنواع السرطانات التي تُشخَّص على مستوى العالم ورابع سبب رئيس للوفاة من السرطان لدى النساء. تحديد مدى تكرار الأورام الخبيثة للجهاز التناسلي للأنثى الموجود في أرشيف علم الأمراض بقسم علم الأمراض بكلية الطب جامعة بنغازي في المدى ما بين الأعوام 2002-2011. أيضا لتحديد نسبة حالات سرطان عنق الرحم مقارنة مع حالات الجهاز التناسلي الأنثوية الأخرى التي تُسَجَّل في الأرشيف. علاوة على ذلك، تُحَدَّد الفئات العمرية ودرجات التمايز المرضية إن أمكن. التحليل النسيجي المرضي بأثر رجعي لحالات السرطان المشخصة من (2002-2011). في أثناء مراجعة الجهاز التناسلي للأنثى لأرشيف الأمراض السرطانية، جُمِعَت جميع حالات سرطان عنق الرحم من 2002-2011 وعددها 330 حالة/عينة وجُمِعَت جميع كتل الأنسجة المضمنة بالفورمالين للمرضى المصابين بسرطان عنق الرحم في تلك الفترة، ومعالجتها من أجل شرائح زجاجية مصبوغة. تحليل 330 حالة سرطان للجهاز التناسلي للأنثى مسجلة في أرشيف علم الأمراض. (52٪) كانوا من سرطان بطانة الرحم وكان هذا هو الأكثر شيوعا. تبع ذلك سرطان عنق الرحم (30.9٪)، وأورام المبيض (13٪)، وأورام المهبل (2٪)، وأورام فالوب وأورام الفرج (1٪). كان النوع الأكثر شيوعًا من سرطان عنق الرحم هو سرطان الخلايا الحرشفية (62٪)، وكان الورم الغدي (31٪) والنوع الأقل شيوعًا هو سرطان الخلايا الحرشفية الغدية (7٪). كان متوسط عمر المرضى 54.67 سنة. عُرِضَت معظم الحالات في فترة ما بعد سن اليأس (62.5٪).

الكلمات المفتاحية: سرطان الجهاز التناسلي للأنثى، سرطان عنق الرحم، أرشيف علم الأمراض، جامعة بنغازي.

Abstract

Female genital tract (FGT) is the most common site for tumors in females. The most common type of (FGT) cancers is cervical, ovarian and endometrial carcinoma. There are other less common tumor's including tumors of the vagina, vulva and fallopian tubes. Cervical cancer is the second most commonly diagnosed cancer worldwide and the fourth leading cause of cancer death in women. To determine the frequency of (FGT) malignancy found at the pathology archive of the Pathology Department at the Faculty of Medicine in the University of Benghazi between the years 2002-2011. Also to define the proportion of cervix cancer cases as compared with other (FGT) that were recorded in the archive. Moreover, to study the histopathological type of cervical cancer, the age groups and at which grades of differentiation are mostly determined. Retrospective histopathological analysis of (FGT) 330 cancer cases diagnosed between (2002-2011). During the reviewing of (FGT) cancer cases of pathology archive all cases of cervical cancer between 2002-2011 were collected and all formalin-fixed paraffin-embedded (FFPE) tissue blocks of the patients with cervical cancer in that period were collected, and processed to stained slides. In an analysis of 330 FGT cancer cases registered in the pathology archive. (52%) were carcinoma of the endometrium and this was the commonest. This was followed by the carcinoma of the cervix (30.9%), ovarian tumors (13%), vaginal tumors (2%), fallopian tumors and vulva tumors (1%). The most common type of carcinoma cervix was squamous cell carcinoma (62%), adenocarcinoma was (31%) and the least common type was adenosquamous carcinoma (7%). The mean age of patients was 54.67 years. Most cases presented at the postmenopausal period (62.5%). Most cases were poorly differentiated (47.1%), followed by moderately differentiated (33.3%) and well-differentiated (17.6%).

Keywords: Female genital tract cancer, cervical cancer, histopathological study, Pathology Archive.

1. INTRODUCTION

Female genital tract malignancies have a worldwide distribution but vary from one region to another. The incidence of FGT cancer is increasing in developing countries because of poor access to medical care and the unavailability of routine screening, ageing, and cancer-associated lifestyle factors such as smoking, obesity and physical inactivity [1,2]. Cervical cancer is a preventable disease because of the availability of screening tools.

The number of cervical cancer cases has reduced around 80% in developed countries as a result of effective programs for the detection and treatment of pre-cancerous lesions [3]. Cervical cancer is the second most common cancer among women worldwide with an expected 528000 new cases and 266000 deaths among women each year. It is almost completely

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preventable if precancerous lesions are recognized and treated early [4].

In north-eastern Libya, cervical cancer formed 1.8% of the total cancers diagnosed at the female oncology clinic, with a median age of fifty years [5]. In the western part of Libya, it constitutes about 1.89% of all female cancers [6]. The most common cervical carcinomas are squamous cell carcinomas (SCC) 70%, followed by adenocarcinomas (AC) 18% and adenosquamous carcinomas (ASC) 4%, with other carcinomas less than 5% [7,8]. There are different types of SCC classified according to the dominant cell type which includes large cell non-keratinizing, large cell keratinizing, small cell type, verrucous squamous carcinoma and papillary squamous carcinoma [9]. Other rare types of SCC include papillary SCC, papillary transitional cell carcinoma, warty carcinoma, basaloid SCC and lympho-epithelioma-like carcinoma and types of AC involve mucinous adenocarcinoma, endometrioid adenocarcinoma and clear cell carcinoma [10].

Carcinogenesis of carcinoma cervix is a multistep process including many genes; one of these is the tumor suppressor gene P53. It has many mechanisms of anticancer function and plays a role in apoptosis. It can activate deoxyribonucleotide (DNA) and it can induce growth arrest by holding the cell cycle at the G1 regulation point on DNA damage recognition, and induce apoptosis. In cervix cancer, there is dysregulation of P53 which is induced by the Human papilloma virus (HPV) and does not mean capacity to apoptosis, but it may indicate differentiation and proliferative status of the tumor cell [11]. There are strong relations between cervix cancer and sexual activity includes early age at first intercourse, multiple sexual partners. Infection with some types of HPV is the greatest risk factor for cervical cancer [12]. Cervical cancer should be staged before initiating treatment. The most widely used staging system is the one developed by the International Federation of Gynecology and Obstetrics (FIGO) [13]. Effective treatment depends on the early diagnosis of cervical cancer [14]. Treatment of the early stage of cervical cancer either with radical hysterectomy and pelvic lymphadenectomy or with primary radiation with chemotherapy [15]. Treatment of advanced-stage tumors are treated with radiation therapy with multi-agent chemotherapy is preferred as it is associated with a higher response rate [15]. Prognosis depends on the stage of cancer. With treatment, 80 to 90% of women with stage I cancer and 60 to 75% of those with stage II cancer are alive five years after diagnosis. Survival rates decrease to 30 to 40% for women with stage III cancer and 15% or fewer of those with stage IV cancer five years after diagnosis [16].

2. MATERIALS AND METHODS

The present study was a retrospective study conducted in the archive of the Department of Pathology at the Faculty of Medicine in Benghazi University. All females diagnosed with genital tract malignancies from the year 2002 to 2011 were included in the study. The total number of cases was 330 cases. Demographic data including age, nationality, type of cancer, site of cancer, and histopathological diagnosis were included in the study. The slides of carcinoma cervix from the year 2002-2011 were gathered and reviewed by histopathologists and diagnoses re-confirmed. Where the slides were missing or sections not properly preserved, paraffin-embedded tissue blocks were retrieved from the archives of the Department of Pathology. New sections were cut by using a rotatory microtome with a steel sharp knife, 3-4µ thick. The paraffin blocks were sectioned into ribbons, then floated on a 37ºC water bath then picked up on a surface of a clean glass slide. The slides with paraffin sections were placed in a 65ºC oven for 20 minutes to melt the excess paraffin wax, leaving the tissue section intact. They were then stained with routine staining (H&E) Hematoxylin and Eosin stains. Then all the slides were reviewed and re-examined by a histopathologist. Data was entered into a Microsoft Excel workbook 2010 and exported to the Statistical Package for the Social Sciences (SPSS) version 22 for the descriptive analysis.

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3. RESULTS

The total number of cases included in this study were 330 cases diagnosed over the period (2002 –2011). Figure 1 shows that the highest frequency of diagnosed malignant tumor cases of FGT was during the year 2006 (n:63, 19.1%), followed by the years 2005 and 2007 where (n:50, 15.2%) of cases were diagnosed. The lowest frequency (n:4, 1.2%) of diagnosed cases was during the year 2002.

Table 1 reveals that the mean age ± standard deviation was 56.39 ± 13.03 years, as the youngest case aged 15 years and the eldest one was 85 years old. The highest proportion of cases (64.2%) were aged 51 years and above, while the cases aged 50 years and less represented (35.8 %) of the cases (Figure 2).

Figure.3 shows that more than half of the cases (52%) were diagnosed as endometrium cancer, followed by cases diagnosed as cancer cervix (30.9%). Ovarian cancer cases represented (13 %) and vaginal tumors (2%). Fallopian tube cases represented (1.1%) and vulva tumors (1%). Table.2 illustrates that a higher proportion of cases aged 50 years and less (52.3%) compared to (47.7%) among cases aged 51 years and above had ovarian cancer. Endometrium cancer was more prevalent among cases aged 51 years and above compared to those aged 50 years and less (73% versus 27% respectively). Vaginal tumors were more prevalent among cases aged 51 years and above compared to cases aged 50 years and less (71% versus 29%). Fallopian and vulva tumors were prevalent only among cases aged 51 years and above. This difference was highly statistically significant (P= 0.001).

Figure.4 illustrates that the highest frequency of diagnosed cervical cancer cases was during the year 2005 (n=21, 20.6%),

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followed by the years 2006 and 2007 where (n=18, 17.6%, n=17, 16.7%) of cases were diagnosed respectively. The lowest frequency (n=2, 2 %) of diagnosed cases was during the years 2002 and 2003. Regarding the age affected by carcinoma cervix, the mean age ± standard deviation was 54.67 ± 10.89 years; the youngest case was aged 29 years and the eldest one was 85 years old, (Table 3). Figure.5 shows that more than half (n=60, 58.8%) of cervical cancer cases had postmenopausal bleeding, while (n=23, 22.6 %) had heavy menstrual bleeding whereas the symptoms of the rest (n=19, 18.6 %) were not known. The most common type of cervical cancer (62%) was the squamous cell type, followed by adenocarcinoma (31%) and the least common type was adenosquamous carcinoma (7%) shown in Figure 6 and Figure 7).

A higher proportion of cervical cancer cases (47.1%) were poorly differentiated, and (33.3%) were moderately differentiated and (17.6%) were well-differentiated (Figure 8 and Figure 9). Figure 10 shows that (95.1%) of cervical cancer cases were primary cervical cancer and (4.9%) of cervix cancer cases were malignant metastatic tumors to the cervix. Figure 11 reveals that the stages of the majority of the cervical cancer cases (94%) were unknown, (3%) of the cases were diagnosed at stage 2, and (2%) were at stage 3 and only (1%) at stage 1. Table 4 reveals that (62.5%) of cases aged 51 years and above compared to (37.5%) of cases aged 50 years and less were poorly differentiated, equal proportions of cases (50%) aged 51 years and above and 50 years and less had well differentiation cervical cancer. This difference was not statistically significant (P= 0.326).

There was no significant statistical difference between cervical cancer cases aged 50 years and less and the other group aged 51 years and above in comparison to the three types (squamous cell, adenocarcinoma and adenosquamous carcinoma cases) (P= 0.899, Table 5). Table 6 shows a higher proportion (53.6%) of cervical cancer aged 51 years and above were of primary origin compared to (46.4%) of cases aged 50 years and less. Cases of secondary origin were all aged 51 years and above. This did not show a statistically significant difference, (P =0.065). Table 7 illustrates that although (66.7%) of cases aged 51 years and above were at stage 2 compared to (33.3%) among cases aged 50 years and less and only one case at stage 3 and it was from the 51 years and above group, this difference was not of statistical significance (P=0.628).

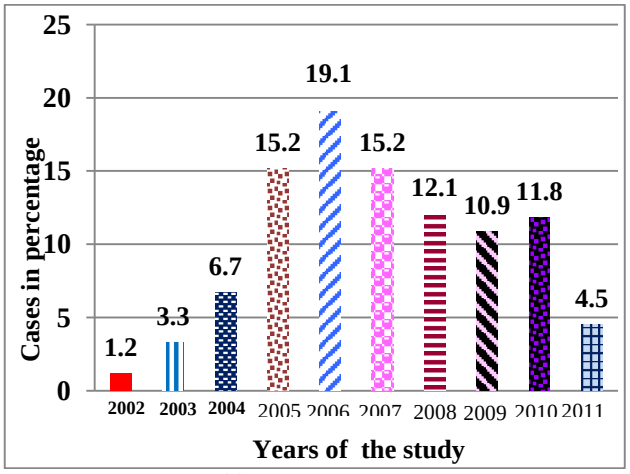
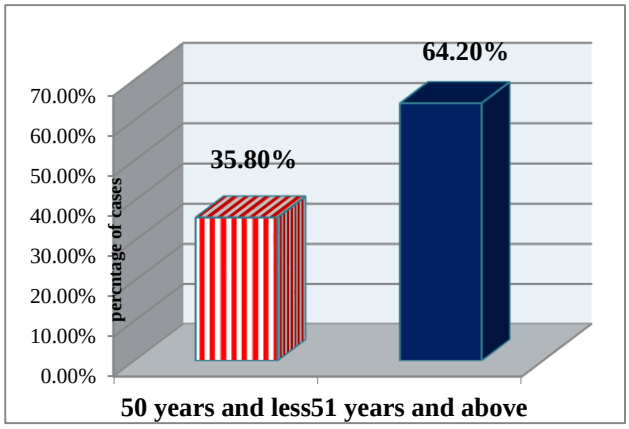


Figure 1: Distribution of female genital tract cancer cases according to the year of diagnosis.

Table 1: Descriptive statistics of age of female genital tract cancer cases.

Type of descriptive statistics	Value (age in years)
Mean	56.39
Median	57.50
Mode	60.00
Std. Deviation	13.03
Range	70.00
Minimum	15.00
Maximum	85.00

Figure 2: Age categories of female genital tract cancer cases.



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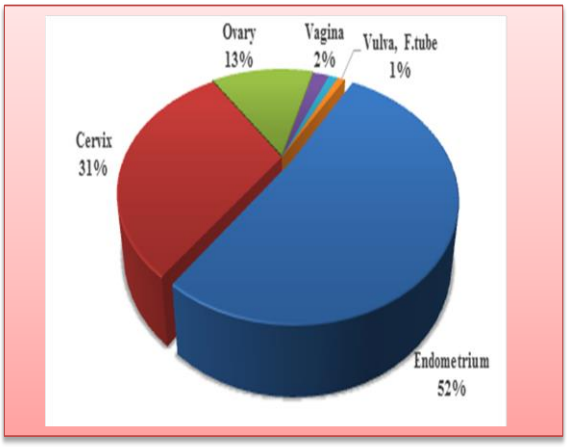


Figure 3: Distribution of female genital tract cancer cases according to their sites.

Table 2.a: Showing the relationship between age categories of FGT cancer cases and site of cancer.

Age categories	Site of cancer					
	Endometrium		Cervix		Ovary	
	No.	%	No.	%	No.	%
50 years and less	46	27.0	47	46.0	23	52.3
51 years and above	124	73.0	55	54.0	21	47.7
Total	170	100.0	102	100.0	44	100.0

Table 2.b: Showing the relationship between age categories of FGT cancer cases and site of cancer.

Age categories	Site of cancer					
	Vagina		Fallopian tube		Vulva	
	No.	%	No.	%	No.	%
50 years and less	2	29.0	0	0.0	0	0.0
51 years and above	5	71.0	4	100.0	3	100.0
Total	7	100.0	4	100.0	3	100.0

(Value =0.001) ***

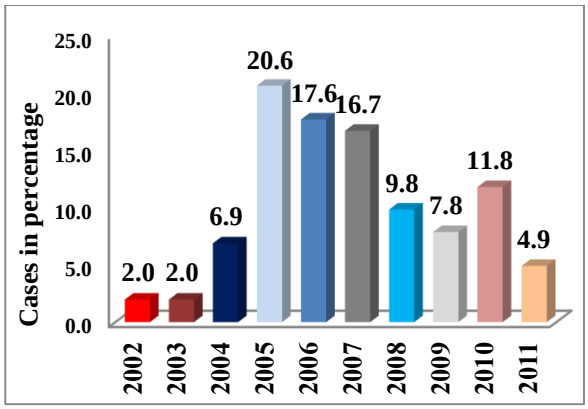


Figure 4: Distribution of cervical cancer according to year of diagnosis.

Table 3: Descriptive statistics of age of cervical cancer cases.

Type of descriptive statistics	Value
Mean	54.67
Median	54.00
Mode	60.00
Std. Deviation	10.89
Range	56.00
Minimum	29.00
Maximum	85.00

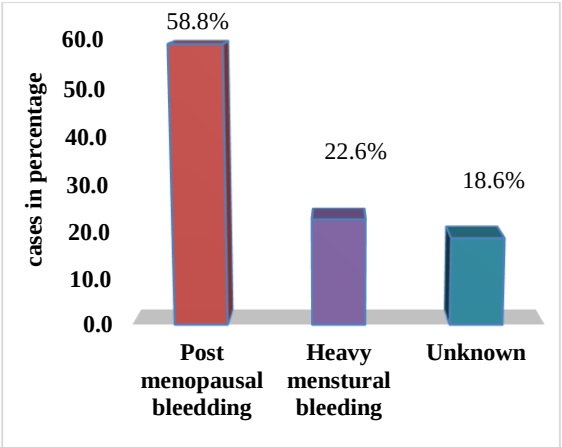


Figure 5: Distribution of cervix cancer cases according to the patient's symptoms.

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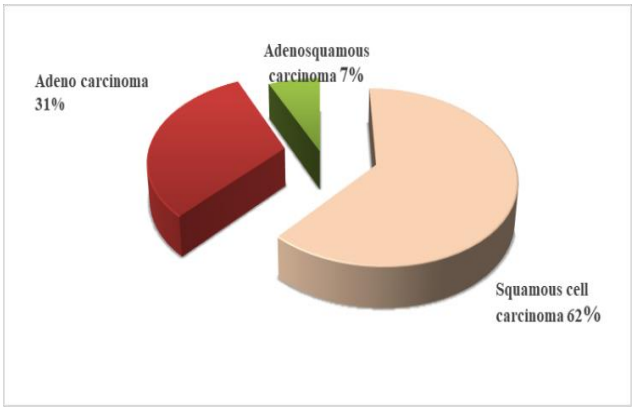
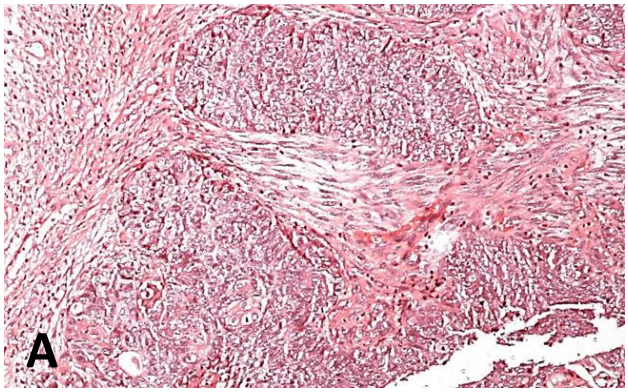
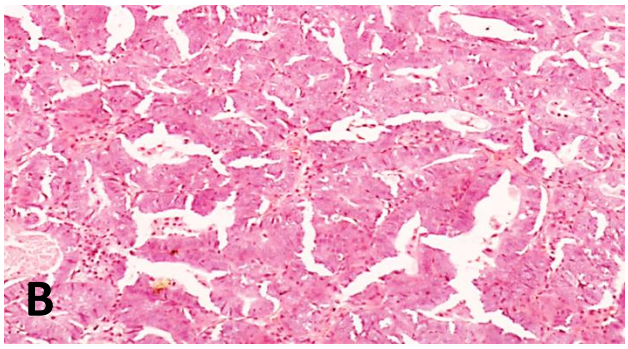


Figure 6: Distribution of carcinoma cervix according to the type.





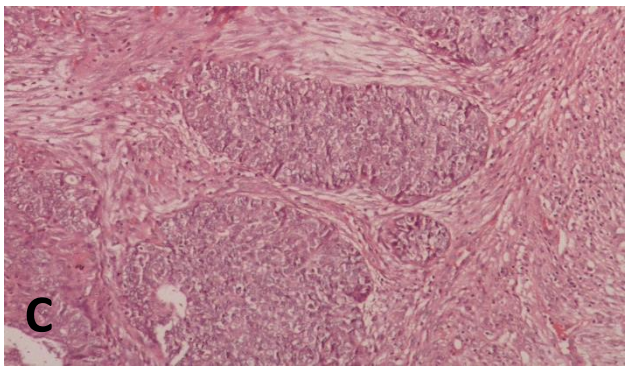


Figure 7: A. Non –keratinizing squamous cell carcinoma, B. Adenocarcinoma cervix. C. Adeno squamous carcinoma cervix. Pathology department, Benghazi University, (H&E stain, X100).

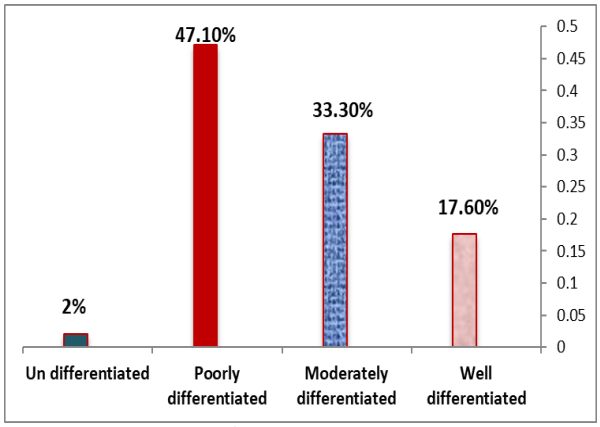
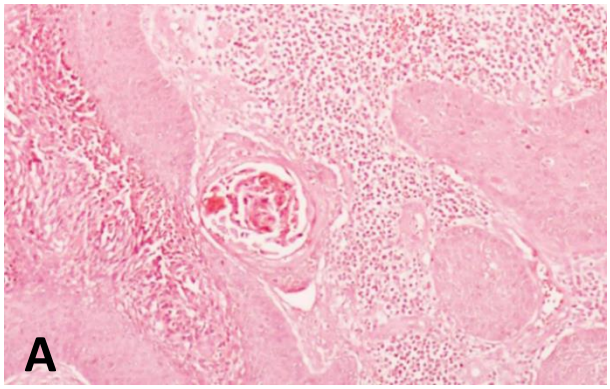
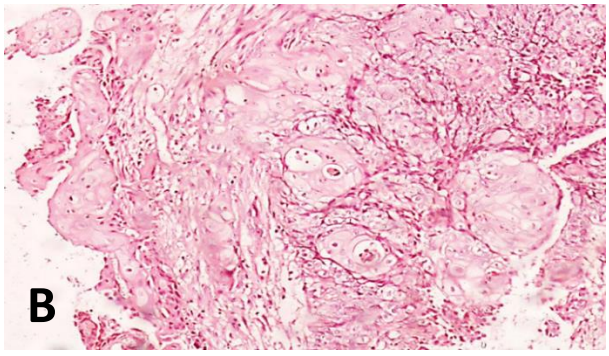


Figure 8: Distribution of cervical cancer cases according to degree of differentiation.





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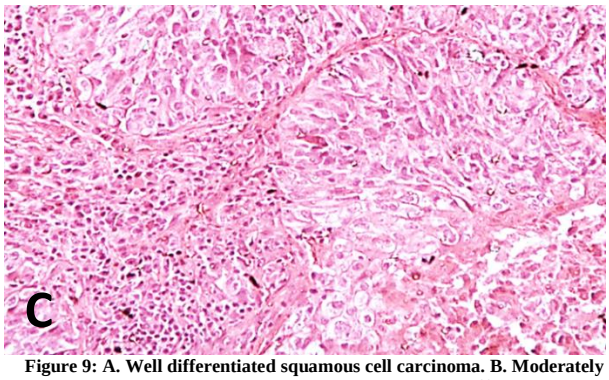


Figure 9: A. Well differentiated squamous cell carcinoma. B. Moderately differentiated squamous cell carcinoma. C. Poorly differentiated squamous cell carcinoma. Pathology Department, Benghazi University, (H&E stain X 200).

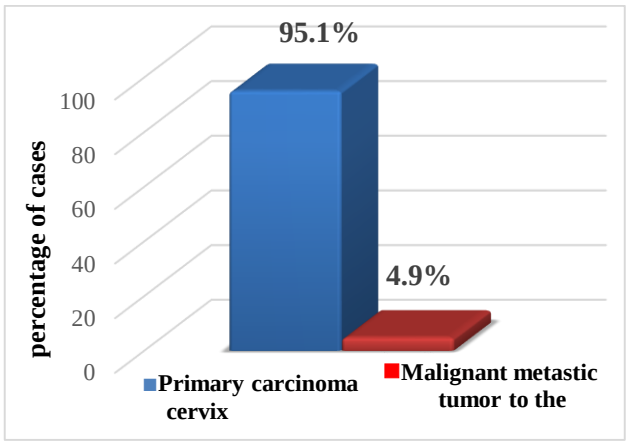


Figure 10: Distribution of cervical cancer cases according to their origin.

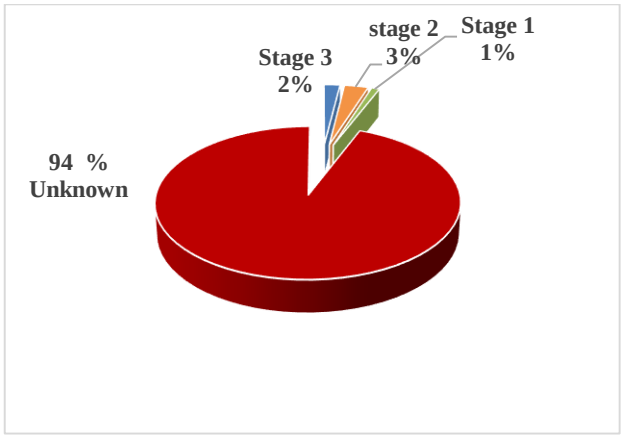


Figure 11: Distribution of cervical cancer cases according to the stage.

Table 4: Relationship between age categories of cervical cancer cases and their degree of differentiation.

Age categories of cervical cancer cases	Degree of differentiation							
	Well differentiated		Moderately differentiated		Poorly differentiated		Un differentiated	
	No	%	No	%	No	%	No	%
50 years and less	9	47.36	18	51.43	18	37.5	0	0.00
51 years and above	10	52.64	17	48.57	30	62.5	2	2%
Total	19	100.0	35	100.0	48	100.0	2	100.0

(P= 0.326).

Table 5: Relationship between age categories of cervical cancer cases and their types.

Age categories	Cervical cancer types					
	Squamous cell carcinoma		Adenocarcinoma		Adeno-squamous carcinoma	
	No	%	No	%	No	%
50 years and less	29	46.0	13	40.6	3	42.9
51 years and above	34	54.0	19	59.4	4	57.1
Total	63	100.0	32	100.0	7	100.0

(P= 0.899).

Table 6: Relationship between age categories of cervical cancer cases and their origin.

Age categories	Origin of cervical cancer cases			
	Primary cervical carcinoma		Malignant metastatic tumor to the cervix	
	No	%	No	%
50 years and less	45	46.4	0	0.0
51 years and above	52	53.6	5	100.0
Total	97	100.0	5	100.0

(P= 0.065).

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Table 7.a: Relationship between age categories of cervical cancer cases and their stages.

Age categories	Stages of cervical cancer cases			
	Stage 1		Stage 2	
	No	%	No	%
50 years and less	0	0.0	1	33.3
51 years and above	1	100.0	2	66.7
Total	1	100.0	3	100.0

Table 7.b: Relationship between age categories of cervical cancer cases and their stages.

Age categories	Stages of cervical cancer cases			
	Stage 3		Unknown	
	No	%	No	%
50 years and less	0	0.0	44	45.8
51 years and above	2	100.0	52	54.2
Total	2	100.0	96	100.0

(P= 0.628).

4. DISCUSSION

During the period under review in this study, the majority of the female genital tract malignancies recorded at the archive of the Pathology Department at the University of Benghazi were from the endometrium (52%) followed by cervical cancer (30.9%), followed by ovarian cancer (13%) and vaginal tumors (2%) and lastly an equal proportion of cases (1%) had either fallopian tumors or vulval tumors which is inconsistent with other studies done in India, and Nigeria where cervical cancer was found to be the most common genital tract malignancy (44.7% and 71%) followed by ovarian cancer (9.1% and 14%) and then endometrium carcinoma (8 % and 7%) respectively. The less common type of cancer of FGT in the current study was due to vaginal and fallopian tube cancers (2%) and (1%) correspondingly, similar to a result that has been previously reported [17, 18].

In this study, the age of patients affected with female genital tract malignancy ranged from 15 years to 85 years with a mean age ± standard deviation of 56.39 ± 13.03 years. Most of the patients were in the age group of 51 years and above (64.2%). A parallel result was seen by a previous study conducted in Ghana where most of the patients were in the age group of 60-69 years (66.4%) with a mean age ± standard deviation of (57.7±13.8) [19].

In this study, cervical cancer formed 30.9% of the total female genital tract cancer recorded at pathology archive from the year 2002-2011, with a median age of 54.67± 10.89 years. In the previous study of the eastern region of Libya using data from 2003 cervical cancer was recorded at 5% of female malignancies, with a median age of 50 years [5]. Another report produced by the Sibratha Cancer Registry in western Libya recorded cervical cancer at 1.89% of all female cancers [6]. A Saudi Arabian study similarly found that cervical cancer comprised 2.5% of the total female malignancies [20]. In Pakistan, it was found that cervical cancer constituted 3.6% of female malignancies, with an average age of 53.27years [21]. The difference in values may be explained by the fact that previous studies collected data for a period of only one year and therefore, natural variations could occur within a single year. This study included data collected from the year 2002 to 2011.

Cervical cancer incidence rates in the U.S.A declined by half between the year 1975 (14.8 per 100,000) and the year 2014 (6.9 per100,000) due to the widespread uptake of screening [22]. Similarly, in this study, the number of cervix cancer cases decreased from the year 2002 to the year 2004. From 2005 to 2008, the number of cases increased and then declined by half between 2009 and 2011. This could be explained by the fact that during the period from 2005 to 2008 most cases of cervical cancer were diagnosed only at the Pathology Department at the Faculty of Medicine in the University of Benghazi while between the period 2009 to 2011, the histopathology centers in Benghazi city multiplied. For this reason, the number of received cervical tissue biopsies decreased Pathology Department at the Faculty of Medicine in the University of Benghazi.

Most of the cervical cancer cases in this study occurred at the age of 47-57 years. This result is in agreement with the study of cervical cancer in north-eastern Libya from the year 2000 - 2008 which showed that the highest incidence was observed in the 45 - 54 years of age group [23]. This is in agreement with previous studies in the UK and Finland which showed that the peak incidence of cervical cancer was detected among women below the age of 50-55 years [24,25], and contrasts with a previous study in Pakistan, which reported that cervical cancer patients were most commonly between 60 and 64 years of age [21].

The most common symptom presented in the files of patients and included in this study was post-menopausal bleeding (58.8%), heavy menstrual bleeding (22.6%) similar to the symptoms of patients with cervical cancer recorded in the American Cancer Society [22], also in agreement with the study of cervical cancer in northeastern Libya between 2000-2008 [23].

A previous study in Korea recorded that the rate of cervical cancer of the young (pre-menopausal) is on the rise, with more and more aggressive forms presenting to oncology clinics [26]. This is inconsistent with this study, which showed that the majority of cases presented were post-menopausal (80.99%). This may be due to fact that elderly women are mostly homemakers that are uneducated and lack knowledge about the disease and the importance of screening programs.

The histopathological findings of this study state that SCC was the most predominant form of cervical cancer (62%) followed by AC (31%) and then ASC (7%). These results collaborate well with a previous study conducted in north-eastern Libya [23] in which SCC was (83.8%) and AC was (16.2%). They are also in agreement with studies done in Pakistan, which showed that the

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most prevalent form of cervical cancer was squamous cell carcinoma (86.5%). On the other hand, this study's results are inconsistent with a previous study in a particular American state that revealed that adenocarcinoma rates have doubled (29.1%), while SCC rates have been decreasing (5.49%) [27]. It is also dissimilar with numerous studies in European countries that reported increasing rates of cervical adenocarcinomas relative to squamous cell carcinomas [28]. This result is due to the facility of cytological screening to effectively detect squamous cell carcinoma in early stages, whereas adenocarcinomas have been reported to be less detectable by screening [29].

In this study, the majority of cervix cancer cases were poorly differentiated or grade III (47.1%). This result is different from the previous study in Pakistan which presented that the majority of cervix cancer cases were moderately differentiated or grade II (45.9%) [21] and corresponds with a preceding study in north-eastern Libya which revealed that the majority of cervical cancer cases presented in grade III or poorly differentiated [23]. Also, this result is in agreement with a Sudanese study which showed that most cervical patients were diagnosed as grade III [30]. This result may be due to a lack of routine screening in Libya and Sudan so the patients presented at a high grade of differentiation.

5. CONCLUSION

This study found that female genital tract cancer cases were more common in relatively middle-aged women (mean age 56.39 years). More than half of the cases (52%) were diagnosed as endometrium cancer, followed by cases diagnosed as cervix cancer (30.9%). The most common type of carcinoma of the cervix was squamous cell carcinoma (62%), adenocarcinoma was (31%) and the least common type was adenosquamous carcinoma (7%). The mean age of patients was 54.67 years of age. Most cases presented were postmenopausal (62.5%). The majority of cervical cancer cases presented with bleeding per vagina. Furthermore, most cases were poorly differentiated (47.1%), and then moderately differentiated approximately (33.3%) and the least in number were well-differentiated (17.6%).

6. RECOMMENDATION

- Public health education, including anti-smoking and healthy lifestyle programmes, as well as awareness of promotions regarding early detection of cancer is very important to reduce cancer mortality.
- Establishing active screening programs in Libya is essential to screen, control and prevent cervical cancer among women. Screening programs would not only assist in decreasing the incidence of cervical cancer, but also in predicting cases at earlier stages, where curative treatments are an option and the long-term prognosis is better.
- Routine use of HPV vaccines (Gardasil and Cervarix) reduce the risk of cancerous or precancerous changes of the cervix and are typically given to young females at the time of puberty.
- Establishment of an electronic archive to facilitate the collection of data for future study.

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