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Evaluation of Radiotherapy Outcomes in Cervical Cancer: A Multicenter Case Series Study from Libya (2019–2022)

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ABSTRACT

Background: The cervical cancer is considered as fourth most common female cancer with estimated frequency was 662,301 new cases annually worldwide particularly in low- and middle-income courtiers (LMICs). The treatment options depend on cervical cancer staging at time of diagnosis which includes surgery interventions, chemoradiation, and combination of both.

Aims: This study aimed to evaluate the radiotherapy outcomes among Libyan women with cervical carcinoma.

Methods and Materials: This study was case series study carried out at multicenter settings included three radiation oncology departments in three different cities in Libya included Tripoli University Hospital, National Cancer Institute Misruata and National Cancer Institute Sabruata between January 2019 and December 2022. The study included adult Libyan women who diagnosed by cervical cancer. The data was collected and analyzed by Statistical Package for the Social Sciences (SPSS) version 24.

Results: In this study, the mean age was 55.59 years ± 12.015 SD, 79.4% (27) were multipara, According to FIGO classifications, 29.4% (10) had stage IB1 followed by 17.6% (6) had stage IIB and similar percentage recognized for stage IIIB. 70.6% (24) had squamous cell carcinoma. And most patients had negative margin resection accounted for 88.2% (30). Half of patients had expressed lymphovascular invasion and lymph node metastasis. About 67.6% (23) had received concurrent chemo radiotherapy while 32.4% (11) had received radiotherapy only because patients were unfit for operation. And 85.3% (29) had received External Beam Radiation Therapy (EBRT) alone while 14.7% (5) had received both EBRT combined with brachytherapy. Acute and late side effects of radiotherapy had been identified. About half of patients had good outcomes followed radiotherapy with five years survival rate for 55.9% (19), out of five cases from those 19 cases had received brachytherapy combined with external beam radiation therapy which found to had statistically significant results (P-value = 0.001).

Conclusion: In this study, the majority of cervical cancer cases had squamous cell carcinoma, which frequently relays between IB1 and IIIB staging, with a high rate of negative margin resection identified. The rate of radiotherapy side effects was reported to be higher among cases who received external beam radiotherapy followed by brachytherapy in comparison to those who underwent external beam radiotherapy alone. Moreover, despite the absence of brachytherapy facilities in our country but the five cases who received it outside the country exhibit good health outcomes with five years survival rate.

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Keywords: Cervical Cancer, Radiotherapy, Concurrent Chemo Radiotherapy, External Beam Radiation Therapy, Brachytherapy, Libya

List of Abbreviations
AC: Adenocarcinoma
ASC: Aden Squamous Carcinoma
BT: Brachytherapy
CCRT: Concurrent Chemo Radiotherapy
EBRT: External Beam Radiation Therapy
FIGO: International Federation of Gynecology and Obstetrics
GGC: General Good Condition
HPV: Human Papillomavirus
IMRT: Intensity Modulated Radiation Therapy
LMICs: Low and Middle-Income Courtiers
PLND: Pelvic Lymph Node Dissection

RT: Radiation Therapy
SCC: Squamous Cell Carcinoma
SD: Standard Deviation
SPSS: Statistical Package for the Social Sciences
TAH: Total Abdominal Hysterectomy
2D: Two-Dimensional
3D: Three-Dimensional

Introduction

Cervical cancer is considered as fourth most common female cancer, with an estimated frequency was 662,301 new cases annually worldwide, particularly in low and middle-income countries (LMICs) [1-2].

Several risk factors are recognized to be linked to cervical cancer, such as high-risk human papillomavirus (HPV) infection, female age, childbirth, use of oral contraception methods, smoking status, and dietary conditions [3-9].

The most frequent oncogenic human papilloma virus (HPV) species, which are responsible for cervical cancer, are 16 and 18 species, reaching 70% of affected cases. And there are three common histopathological characteristics of cervical cancer are Squamous cell carcinoma (SCC), adenocarcinoma (AC), and Aden squamous carcinoma (ASC) account for 95% [10-13].

By 2018, the International Federation of Gynecology and Obstetrics (FIGO) had updated the cervical cancer staging guidelines classifications with some significant alterations. In stage I disease, the stage IA describes the lesion not to be includes a lateral size extension criteria while the stage IB is divided into three subgroups according to diameter measurements including IBI (≥5 mm to <2 cm), IB2 (≥2 to <4 cm) and IB3(≥4 cm). And the stage III disease currently includes stage IIIC1 and IIIC2 extend to pelvic or para-aortic lymph nodes, respectively [14].

The treatment options depend on cervical cancer staging at the time of diagnosis, which includes surgery interventions, chemoradiation, and a combination of both [15].

Over the last two decades, the advancement of treatment modalities has significantly improved cervical cancer outcomes in terms of increased survival rates and reduced toxicity issues. Radiation therapy (RT) has developed from two-dimensional (2D) to three-dimensional (3D), embraced external beam radiation therapy (EBRT) and brachytherapy (BT) [16].

Several randomized control trials had revealed that the combination of radiation with concurrent platinum-based chemotherapy had beneficial effect in increasing the survival rate at five years to 10% in compared to radiotherapy alone for women with stage IB3-IVA cervical cancer but close precaution and special laboratory monitoring most be considered to stop chemotherapy before completion of five cycles to prevent possible adverse effects such as neutropenia, anemia, and thrombocytopenia [17-19].

Therefore, the aim of the present study was to evaluate the radiotherapy outcomes among Libyan women with cervical carcinoma.

Methods and Materials

This study was case series study carried out at multicenter settings included three radiation oncology departments in three different cities in Libya included Tripoli University Hospital in Tripoli (The city is capital of Libya), National Cancer Institute Misurata in Misruata city (city located in central Libya) and National Cancer Institute Sabruata in Sabruata (city located in western Libya) between January 2019 and December 2022.

The study included adult Libyan women who diagnosed by cervical cancer, which fit the diagnostic criteria of FIGO classifications (2018) along with histopathological evaluation and all patients had received standardized radiotherapy protocols included three dimension approach of intensity modulated radiation therapy (IMRT) with used dose ranged between 45 – 50.5 Gray [14].

The data was collected by three clinical investigator which entered the data into standardized validated questions in excel sheet form then transferred into Statistical Package for the Social Sciences (SPSS) version 24 for summarization and interpretation of results into descriptive analysis included frequency, percentage, mean and standard deviation as well as inferential analysis were performed included Chi square test and student t test to determine the statistical differences between specific variables with consider the P-value of less than 0.05 as statistical significant results.

Results

A thirty four Libyan women who diagnosed by cervical cancer at three district centers in Libya during 2019 and 2022 were included in this study. thirteen cases located in Tripoli, fourteen cases located in Mistruata and seven cases located in Sabruata. The mean age was 55.59 years ± 12.015 SD and the most frequent age ranged between 50 and 59 years accounted 32.4% (11) followed by 26.5% (9) of them were ranged between 60 and 69 years. (Table 1)

Table 1: Distribution of Age, Multicenter, Libya, 2019-2022

Variables (n = 34)	N	%
30 - 39 years	4	11.8%
40 - 49 years	6	17.6%
50 - 59 years	11	32.4%
60 - 69 years	9	26.5%
70 - 79 years	3	8.8%
> 80 years	1	2.9%

Almost of cases were still married accounted for 82.4% (28) while just 17.6% (6) of them were divorced. (Figure 1)

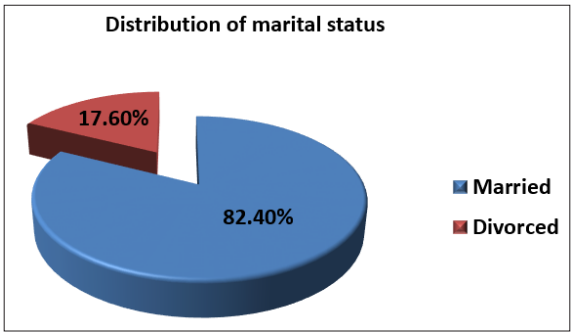

Figure 1: Distribution of Marital Status, Multicenter, Libya, 2019-2022

About 79.4% (27) of cases were multipara accounted for while 20.6% (7) of them were nullipara. (Figure 2)

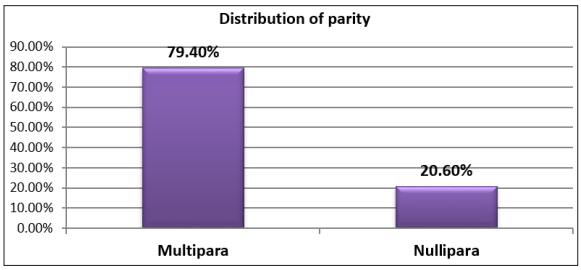

Figure 2: Distribution of Parity, Multicenter, Libya, 2019-2022
About 35.3% (12) of patients had expressed diabetes mellitus and 29.4% (10) of them had expressed hypertension, none of cases were smoker.

According to FIGO classifications, 29.4% (10) of cases had stage IB1 followed by 17.6% (6) of them had stage IIB and similar percentage had recognized for stage IIIB (Table 2).

Table 2: Distribution of FIGO Classifications According to the Patients at Time of Diagnosis, Multicenter, Libya, 2019-2022

Variables (n = 34)	N	%
IA1	2	5.9%
IB1	10	29.4%
IIA1	3	8.8%
IIA2	1	2.9%
IIB	6	17.6%
IIIA	3	8.8%
IIIB	6	17.6%
IVA	1	2.9%
IVB	2	5.9%

Based on histopathology results, 70.6% (24) of cases had squamous cell carcinoma while 29.4% (10) of them had adenocarcinoma (Figure 3).

And most of patients had negative margin resection accounted for 88.2% (30) with just 11.8% (4) of them had positive margin.

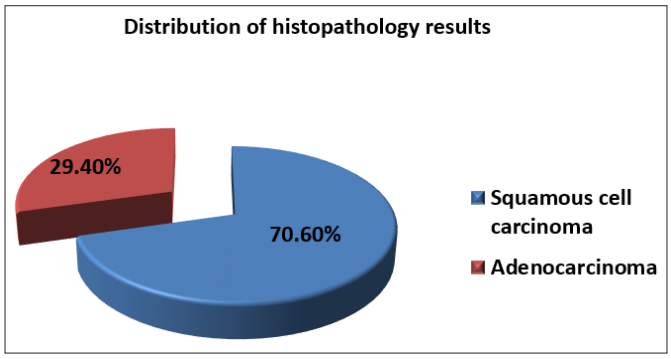

Figure 3: Distribution of Histopathology Results, Multicenter, Libya, 2019-2022

Half of patients had expressed lymphovascular invasion and lymph node metastasis with 20.6% (7) had pelvic lymph node dissection (PLND) and 14.7% (5) had total abdominal hysterectomy (TAH) with pelvic lymph node dissection (PLND). (Table 3)

Table 3: Distribution of Surgery Outcomes, Multicenter, Libya, 2019-2022

Variables (n = 34)	N	%
Inoperable	22	64.7%
PLND	7	20.6%
TAH+PLND	5	14.7%
IIA2	1	2.9%

About 67.6% (23) of cases had received concurrent chemo radiotherapy (CCRT) while 32.4% (11) of them had received radiotherapy only because patients were unfit for operation. (Figure 4)

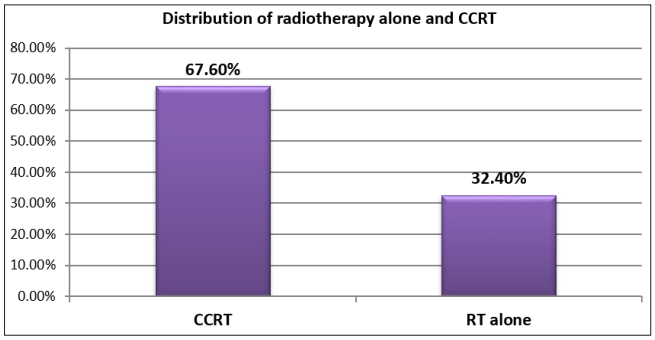

Figure 4: Distribution of Radiotherapy alone and CCRT, Multicenter, Libya, 2019-2022

And 85.3% (29) of cases had received External Beam Radiation Therapy (EBRT) alone while 14.7% (5) of them had received both EBRT combined with brachytherapy (Figure 5).

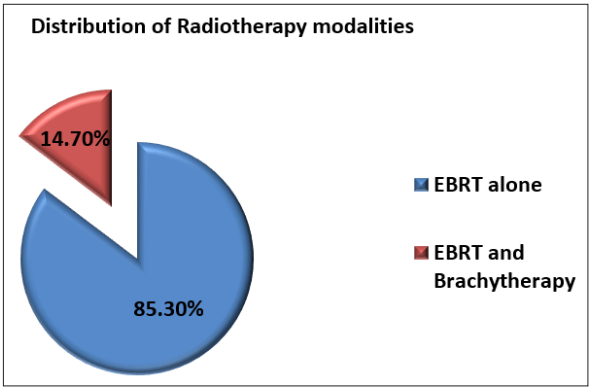

Figure 5: Distribution of Radiotherapy Modalities, Multicenter, Libya, 2019-2022

Based on acute side effects of radiotherapy, 52.9% (18) had vaginitis, 47.1% (16) had colitis, 35.3% (12) had moist desquamation, 32.4% (11) had cystitis and 26.5% (9) had nausea (Table 4).

Table 4: Distribution of Acute Side Effects of Radiotherapy, Multicenter, Libya, 2019-2022

Variables (n = 34)	Yes	No
Vaginitis	52.9% (18)	47.1% (16)
Colitis	47.1% (16)	52.9% (18)
Moist desquamation	35.3% (12)	64.7% (22)
Cystitis	32.4% (11)	67.6% (23)
Nausea	26.5% (9)	73.5% (25)

Based on late side effects of radiotherapy, 23.5% (8) had vaginal stenosis and 20.6% (7) had urethral stricture (Table 5).

Table 5: Distribution of Late Side Effects of Radiotherapy, Multicenter, Libya, 2019-2022

Variables (n = 34)	Yes	No
Vaginal stenosis	23.5% (8)	76.5% (26)
Urethral stricture	20.6% (7)	79.4% (27)

Statistical significant differences had established in relationship between histopathological results and treatment outcomes which revealed that the concurrent radiotherapy approaches were superior in compare to radiotherapy alone approach in both squamous cell carcinoma and adenocarcinoma cases. (P-value = 0.005) (Figure 6).

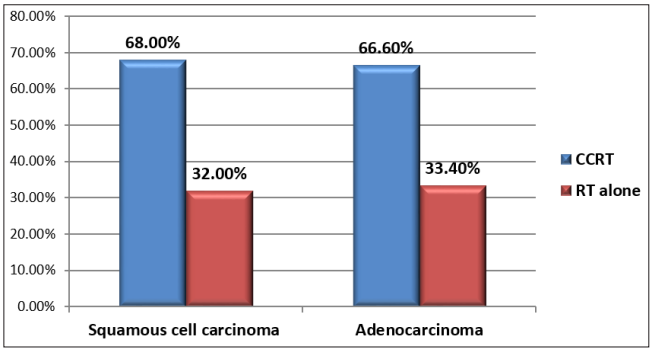

Figure 6: Distribution the Relationship between Histopathological Results and Treatment Outcomes, Multicenter, Libya, 2019-2022

Also, statistically significant differences were reported in the relationship between histopathological results and radiotherapy modalities, which showed that the brachytherapy combined with external beam radiation therapy was superior compared to external beam radiation therapy alone, mainly among squamous cell carcinoma cases, only accounted for 20.0% (Five cases). (P-value = 0.014) (Figure 7).

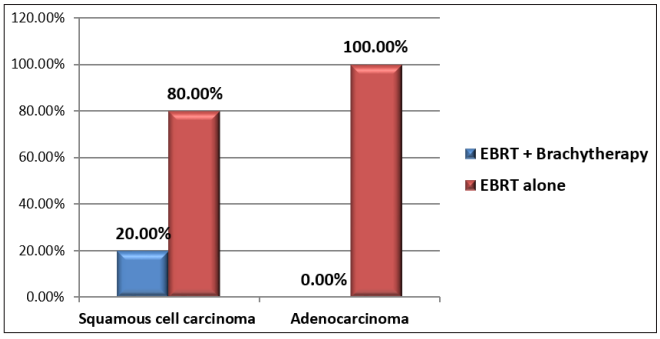

Figure 7: Distribution the Relationship between Histopathological Results and Radiotherapy Modalities, Multicenter, Libya, 2019-2022

About half of patients had good outcomes followed radiotherapy with five years survival rate for 55.9% (19), out of five cases from those 19 cases had received brachytherapy combined with external beam radiation therapy which found to had statistically significant results (P-value = 0.001).

While just 14.7% (5) of them had recurrent of cancer, 17.6% (6) of them had died and 11.8% of them had missed follow up. (Table 6)

Table 6: Distribution of Patients Outcomes, Multicenter, Libya, 2019-2022

Variables (n = 34)	N	%
Alive with GGC	19	55.9%
Died	6	17.6%
Missed follow up	4	11.8%
Recurrence	5	14.7%

Discussion

It is well known that the radiation therapy exhibits a crucial role in the treatment of cervical cancer. And various meta-analyses studies have found that the concurrent chemo radiotherapy (CCRT) approach is the standard definitive therapy for IB3-IVA stages [20]. For this context, this study assessed the radiotherapy outcomes among Libyan women with cervical carcinoma at three multicenter Libyan hospitals between 2019 and 2021.

In the current study, 67.6% of cases had received CCRT but only five cases had received brachytherapy combined with EBRT, those cases had exhibit significant good health outcomes in terms of five-year survival rate and low recurrent of cancer. These results are supported by a meta-analysis done via Ma S et al (2019), which showed that the CCRT could be rise the patients survival in those with better performance status [21].

The radiotherapy modalities is still growing in Libya with a small number of Libyan radiation oncologists exist. Despite, this shortage and the absence of a brachytherapy approach in our country, but all cases are advised to take the brachytherapy outside this country to achieve optimal treatment outcome, Moreover, most cases had difficulty to take brachytherapy because of financial burden, disease status, and fears of side effects.

This condition is not only unique for Libyan society but also exists in most low- and middle-income countries that have a deficit of radio- therapy facilities despite the ultimate requirement in comparison to high- resource countries. Moreover, improving the radiotherapy staff and providing effective training programs to enhance the number of radiotherapists, radiation oncologists, radiation physicists, and specialized nurses are required to increase the standard quality of health care [22-24].

Although, the advancement in combined chemotherapy and concurrent radiation but it still has potential side effects and toxic hazards. However, a literature study had suggested that the rate of severe adverse reactions will be low if the drugs are well administered and tolerated. Also, it has been detected that the radiotherapy duration is considered as an independent prognostic factor influencing the survival rate and disease control status, particularly is poor among cases who receive radiotherapy for more than 60 days [25-27].

Additionally, the substandard treatment protocols will contribute to the low survival rate of cervical cancer by introducing most

cases in late advanced stages like in our society. Thence, most cases were found to require palliative radiotherapy and shorter waiting time to overcome the disease outcome. This condition is widely common in many sub-Saharan African countries which Libya belongs to them [28-33].

The limitation of the study was limited use of brachytherapy and deficient of those clinics that may affect study results. While the strength of the study was multicenter study approach.

Conclusion

In this study, the majority of cervical cancer cases had squamous cell carcinoma, which frequently relays between IB1 and IIIB staging, with a high rate of negative margin resection identified. The rate of radiotherapy side effects was reported to be higher among cases who received external beam radiotherapy followed by brachytherapy in comparison to those who underwent external beam radiotherapy alone. Moreover, despite the absence of brachytherapy facilities in our country but the five cases who received it outside the country exhibit good health outcomes with five years survival rate. So, we recommended a combined EBRT and brachytherapy approach to all cases of cervical cancer to achieve good outcomes and enhance the survival rate. This point requires integrated national strategy programs to implement brachytherapy clinics, along with the improvement of radiotherapist and radiation oncologist skills, to sustain this approach.

Ethical Approval

This study was ethical approved from the selected hospitals with obtain strict privacy of patient's data and used for research purpose only.

Conflict of Interest

The authors did not have any type of conflict of interest regarding publishing this study.

Acknowledgment

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