Research Article

Treatment outcomes and prognostic factors of cervical cancer at South Egypt Cancer Institute

Abstract

Background: The aim of this retrospective study was to analyse the clinicopathological factors of cervical cancer and its prognostic significance, various treatment adopted and their outcome in our local sitting.

Methods: From January 2005 to December 2013, a total of 83 patient records were analyzed. As initial treatment, 16 patients underwent surgical resection and 61 patients received definitive radiotherapy, the remaining 6 patients had stage IV disease and received palliative treatment. Among 61 patients received definitive radiotherapy, forty six patients received chemotherapy concurrently with radiotherapy and external beam boost was given to 43 patients while brachytherapy boost was given to 18 patients. Thirteen patients had residual disease after definitive radiotherapy, nine of whom underwent salvage surgery and the remaining 4 patients were inoperable and received palliative treatment. A total of 16 operated patients received radiotherapy due to presence of risk factors.

Results: After median follow up period of 54 months (range = 8-108 months), treatment failed in 37 patients (48.0%). The pattern of failure included isolated local recurrence in 21 patients (27.3%), isolated distant metastasis in 13 patients (16.9%) and mixed in 3 patients (3.9%). The 5-year overall survival (OS) and disease free survival (DFS) were 53.7% and 46.3% respectively. In univariate analysis, tumor size (p=.033), stage (p=.001) and type of initial treatment (p=.034) were significant prognostic factors for OS while clinical stage was the only statistically significant prognostic factor for DFS (p=.009). In multivariate analysis, advanced stage was independent prognostic factor for poor OS (p=.001) and DFS (p=.003).

Conclusion: Most of cervical cancer patients at our Institute were seen at late stage which reflects lack of effective cervical screening program and necessitating the need for organized referral system to regional center to ensure optimal combined treatment.

Keywords: cervical cancer, chemoradiation, prognostic factors, radical hysterectomy

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Introduction

Cervical cancer is one of the common gynecological malignancies, with nearly 500,000 newly diagnosed cases each year of which more than 90% in developing countries.[1] The highest incidence of cervical cancer occurs in Central and South America, Eastern Africa, South and South-East Asia, and Melanesia.[2] Invasive cervical cancer is the most common cause of cancer deaths in Africa accounting for 10.4%, which represents one in five of all cancer deaths in African women.[3]

The main reasons for higher incidence and mortality of the cervical cancer in developing countries include lack of awareness of cervical cancer in the general population and health care providers and lack of effective screening program to detect and treat early stage of the disease.[4] There are many clinicopathological factors affecting recurrence in cervical cancer which become the main reason for decreased survival rate and these include, clinical stage, histological grade, and treatment adopted.[5,6]

In developing countries, few studies are available describing the incidence of cervical cancer, disease stage, management and treatment outcome of these patients.[7,8] Therefore the aim of this study is to establish the database of patients with cervical cancer taking into account the clinicopathological pattern of cervical cancer, highlight different treatment modalities adopted in the management of this disease in our local setting and its effect on disease free survival and overall survival, and evaluate clinicopathological risk factors affecting treatment outcome and survival.

Patients and methods

This retrospective hospital based study included 83 patients diagnosed with cervical cancer and presented to South Egypt Cancer Institute (SECI) from January 2005 to December 2013. The clinical records of these patients were retrospectively analyzed and the following variables were recorded: age, sign and symptoms, parity, histopathology including squamous cell carcinoma or adenocarcinoma, stage based on International Federation of Gynaecology and Obstetrics classification[9] (IA-IVB), grade (well, moderate, poor), primary treatment plan (Surgery, radiotherapy or both),the date of diagnosis and last follow up visit and treatment outcomes (date and site of relapse, date of death). Out of 83 patients, 6 patients presented with stage IVB cervical cancer and they were excluded from survival analysis.

Treatment

Therapeutic strategies were selected for individual patients. In stage I-IVA patients, various treatments such as the combination of surgery and radiotherapy, and chemoradiation therapy were used. Stage IVB patients, various treatment combinations of chemoradiation, palliative radiotherapy, palliative chemotherapy and best supportive care were used.

For surgery, radical hysterectomy with pelvic lymphadenectomy was performed in some patients while pelvic excentration was performed in others. Radiotherapy was given to patients either definitively or postoperatively; patients with deep muscular involvement, vascular invasion, tumor diameter larger than 4 cm, positive lymph node or positive surgical margin were treated with postoperative radiotherapy with or without concurrent chemotherapy. Patients received definitive radiotherapy, whole pelvic irradiation using external beam radiotherapy with 10–15 MV photon of 1.8 Gy per fraction, 5 times per week for a total dose of 50.4 Gy. After external beam radiotherapy, patients were assessed for possibility of intracavitary application. If possible, patients received intracavitary brachytherapy to a total dose of 30Gy / 6 Gy per fraction. Patients with parametrial infiltration, received parametrial boost of 10 Gray in 5 fractions with central blocking. If intracavitary brachytherapy was not possible, additional dose of external beam radiotherapy was given to a total dose of 60 Gy. Postoperative radiotherapy was delivered to a total dose of 50.4 Gy/ 5 fractions per week. During concurrent chemoradiation blood transfusion were allowed to keep hemoglobin level ≥10g/dl. Chemotherapy dose was reduced to 30mg/m^2 when patients developed grade 1 or 2 hematological toxicity and it was held in case of grade 3 or 4 hematological toxicity.

Follow up

After treatment, all patients were followed up regularly every 3 months in the first 2 years and every 6 months thereafter by history and pelvic bimanual examinations to assess response to treatment. Chest x-ray, computerized tomography (CT) scan of the pelvis and abdomen of the pelvis were done every 6 months in the first year and yearly thereafter. Persistent or recurrent disease was documented by imaging studies or biopsy if possible.

Treatment related toxicity was assessed weekly during treatment and at the time of each visit using National Cancer Institute Common Terminology Criteria for Adverse Effect v 3.0.[10]

Statistical analysis

DFS was measured from the date of diagnosis to the date of local recurrence, or distant metastasis or last follow up. OS was measured from the date of diagnosis to the date of death from any cause or to the date of the last follow-up. DFS and OS curves were estimated using the Kaplan–Meier method.[11] Survival data between groups were compared with the Log rank test for univariate analysis and Cox regression analysis for multivariate analysis. The 95% confidence interval (CI) was calculated for the risk ratios for each of the significant prognosticators. All P values <0.05 considered to be significant. All analyses performed using the Statistical Package for Social Sciences software, SPSS, version 18.0 (SPSS inc. Chicago, Illinois, USA).

Ethical considerations

Data were stored securely and made available only to persons conducting the study. All patients participated in this study were coded in numbers instead of names. Treatment decision was approved by institutional review board at our center.

Results

The characteristics of 83 patients with cervical cancer were listed in Table 1. The age of the patients ranged from 28-75 years with a median age of 55 years. Vaginal bleeding (Postcoital, intermenstrual, or postmenopausal) was the most common presenting symptom which was reported by 63patients (75.9%). Squamous cell carcinoma was the most common histopathological tumor and it was encountered in 77 patients (92.8%). According to the FIGO classification, the majority of the patients (42.2%) presented with stage III disease.

Treatment

Surgery

Out of 77 patients (stage IB-IVA), 16 (20.8%) patients underwent primary surgical resection. Radical hysterectomy and pelvic lymphadenectomy was performed in 15 patients and only one case (1.3%) underwent posterior pelvic excentration.

Combined modality

Sixty one patients (79.2%) out of 77 patients (stage I-IVA) received external beam radiotherapy as an initial phase of treatment. External boost radiotherapy was given to 43 patients (70.5%) and brachytherapy boost to 18 patients (29.5%). Concurrent chemotherapy was given to 46 patients (75.4%). The remaining 15 patients (24.6%) were ineligible to receive chemotherapy concurrently with radiotherapy due to renal impairment and treatment related toxicity.

Out of 61 cases received definitive radiotherapy, 13 patients (21.3%) had residual or progressive disease after the whole course of radiotherapy (11 patients received external beam radiotherapy as a boost and 2 patients received brachytherapy as a boost). Nine out of 13 patients, underwent salvage radical hysterectomy and pelvic lymphadenectomy, while the remaining 4 patients were inoperable and received palliative chemotherapy and they died. Four out of 6 stage IVB patients received palliative chemotherapy and or palliative radiotherapy. The remaining 2 cases presented with para aortic lymph node as the only site of metastasis and received definitive chemoradiotherapy.

Adjuvant therapy

A total of 16 operated patients (20.8%) received whole pelvic external radiation within 1 month of surgical resection and 3 of them received neoadjuvant chemotherapy. Adjuvant chemoradiotherapy was given as a result of positive surgical margins in4 patients (25%), positive pelvic lymph nodes in 4 patients (25.0%) and parametrial invasion in 5 patients (31.2%). Adjuvant radiotherapy was given in tumor diameter larger than 4 cm in 7 patients (43.7%), deep stromal invasion in 5 patients (31.2%) and lymphovascular space invasion in 2 patients (12.5%) (Table 1).

Pattern of failure after treatment and follow up

After median follow up period of 54 months (range=8-108 months), treatment failed in 37 patients (48.0%) out of 77 patients with stage IB through IVA cervical cancer. The patterns of treatment failure were, isolated local recurrence in 21 patients (27.3%), isolated distant metastasis in 13 patients (16.9%) and local recurrence with distant metastasis in 3 patients (3.9%) (Table 2).

Among 21 patients who developed isolated local recurrence, 12 patients were candidate for surgical resection. Pelvic excentration was performed in 9 patients while radical hysterectomy was performed in 3 patients. The remaining 9 cases with isolated local recurrence were inoperable and received palliative chemotherapy. Five out of 12 patients with surgically removed isolated local recurrence were alive and free of the disease, and the remaining 7 patients died from surgical complications. All 9 inoperable cases had progressive disease with poor general conditions that required best supportive care and they died.

Table 1 Characteristics of 83 patients with cervical cancer

Variable	Number	Percentage
Age	55	45.8
Median	28 - 75	54.2
Range	38	
< 50	45	
≥ 50		
Duration of Symptoms	8	
Mean	2 – 48	
Range		
Pretreatment Hemoglobin Level	34	41
< 10 g/dl	49	59
≥ 10 g/dl		
Symptoms	38	45.8
Vaginal Bleeding	15	18.1
Vaginal Discharge	9	10.8
Vaginal Bleeding & Urinary Symptoms	6	7.2
Urinary symptoms	16	19.3
Pain & vaginal bleeding		
Histology	77	92.8
Squamous cell carcinoma	6	7.2
Adenocarcinoma		
Tumor Size	21	25.3
≤ 4 cm	62	74.7
> 4 cm		
Lymph Node Metastasis	53	63.9
Negative	30	36.1
Positive	1	1.2
FIGO Stage	9	10.8
IB1	6	7.2
IB2	20	24.1
IIA	7	8.4
IIB	28	33.7
IIIA	6	7.2
IIIB	6	7.2
IVA		
IVB		
Grade	9	10.8
Well Differentiated	34	41
Moderately Differentiated	40	48.2
Poorly Differentiated		
Treatment Modality Adopted	16	19.3
Surgery:		
a. Radical Hysterectomy and Pelvic Lymphadenectomy (15 patients)		
b. Pelvic Excentration (1 patient)	63	75.9
c. Neoadjuvant Chemotherapy (3 patients)	4	4.8
d. Adjuvant Chemoradiotherapy (16 patients)		
Definitive Chemoradiotherapy		
Palliative Radiotherapy &/or Chemotherapy		

Table 2 Pattern of treatment failure of 77 patients (stages IB1-IVA) with cervical cancer

| Variables	Number	Percentage
Total Recurrences	37	48
Isolated LR	21	27.3
Total DM	16	20.8
Isolated DM	13	16.9
DM + LR	3	3.9
Site of DM		
Paraortic Lymph Nodes	3	
Liver	4	
Lung	3	
Liver & Paraortic Lymph Nodes	3	
Lung & Paraortic lymph Nodes	1	
Liver & Bone	1	
Lung & Bone	1	

Abbreviations: EBRT, external beam radiotherapy; CT, chemotherapy; Brachy, brachytherapy

The number of distant metastasis was one in 10 patients while 6 patients had 2 sites of distant metastases. The sites of distant metastases included para aortic lymph nodes in 7 patients (9.1%), liver metastases in 8 patients (10.4%), lung metastasis in 5 patients (6.5%), and bone metastasis in 2 patients (2.6%). Patients who developed isolated distant metastasis and local recurrence with distant metastasis received palliative radiotherapy and or chemotherapy. All of metastatic cases died of their disease.

Survival

The 5-year OS and DFS of the 77 patients (excluding stage IVB patients) with cervical cancer were 53.7% (95% CI 62.3% to 79.9%) and 46.3% (95% CI 50.7% to 70.8%) respectively (Figur[1]es 1 & 2). There were no treatment related deaths.
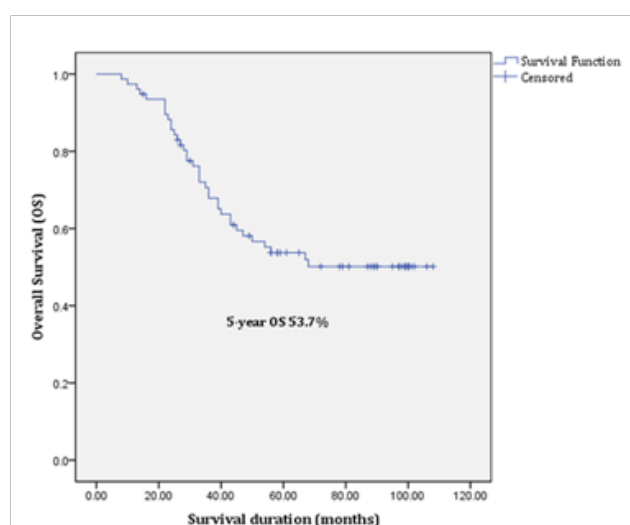
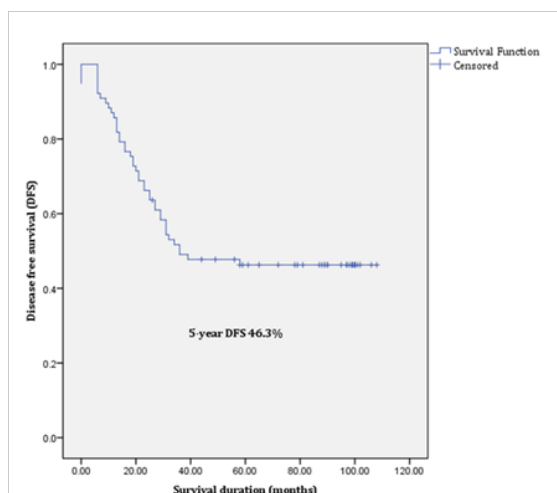**Figure 1** 5-year overall survival of 77 patients with cervical cancer.

Figure 2 5-year disease free survival of 77 patients with cervical cancer.

Prognostic factors for survival

Prognostic factors, such as age, pretreatment hemoglobin level, histology, tumor size, lymph node involvement, FIGO stage, grade and type of initial treatment adopted were analyzed. On univariate analysis, tumor larger than 4 cm (P =0.033), advanced stage (p= 0.001) and surgical resection as an initial treatment (p= 0.034) showed statistically significant decrease in OS. Patients with advanced stage (p= 0.009) had statistically significant poor DFS on univariate analysis (Table 3). Multivariate analysis showed that advanced stage was the only independent prognostic factor for poor OS and DFS; (HR= 3.237; 95% CI= 1.609-6.513; p= .001) and (HR= 2.694; 95% CI= 1.406-5.161; p= 0.003) respectively. Figure 3 & 4 showed Kaplan-Meier analysis of overall survival and disease free survival according to stage.

Table 3 Univariate analysis for DFS and OS in 77 patients with cervical cancer

Variables	5-Year Survival Rates (%)	
	DFS	OS
Age	40.7	48.9
< 55 (n=36)	51.2	58
≥ 55 (n=41)	P= 0.37	P= 0.22
Pretreatment Hemoglobin Level	39.1	48.6
< 10 (n=32)	51.1	56.9
≥ 10 (n=45)	P= 0.44	P= 0.49
Histology	48.8	57.1
Squamous Cell Carcinoma (n= 71)	16.7	16.7
Adenocarcinoma (n= 6)	P= 0.12	P= 0.09
Tumor Size	57.1	73.5
≤ 4cm (n= 21)	42.1	47.1
> 4 cm (n= 56)	P= 0.28	P= 0.033
Lymph Node Metastasis	45.4	56.9
Negative (n= 52)	48	47.7
Positive (n= 25)	P= 0.96	P= 0.57
FIGO stage	90	88.9
I (n= 10)	50	61.7
II (n= 26)	36.7	45.5

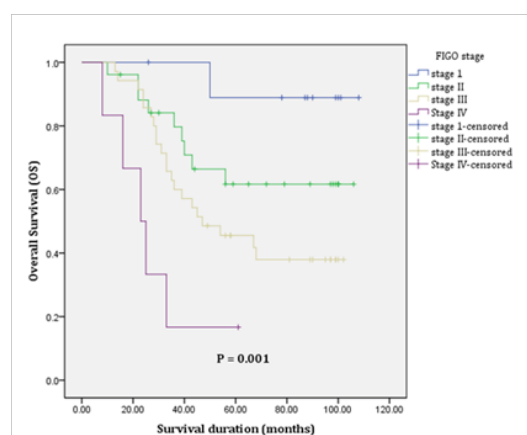| Variables	5-Year Survival Rates (%)	
III (n= 35)	16.7	16.7
IV (n= 6)	P= 0.009	P= 0.001
Grade	33.3	44.4
Well Differentiated (n= 9)	49	62.4
Moderately Differentiated (n= 32)	47.2	49
Poorly Differentiated (n= 36)	P= 0.79	P= 0.39
Initial Treatment Adopted	68.2	71.8
Surgery (n= 16)	27.3	30.3
-EBRT alone (n=11)	34.1	38.4
-CT+EBRT (n=32)	50	50
-EBRT + Brachy (n=4)	64.3	69.3
-CT+EBRT+ Brachy (n=14)	P= 0.07	P= 0.034

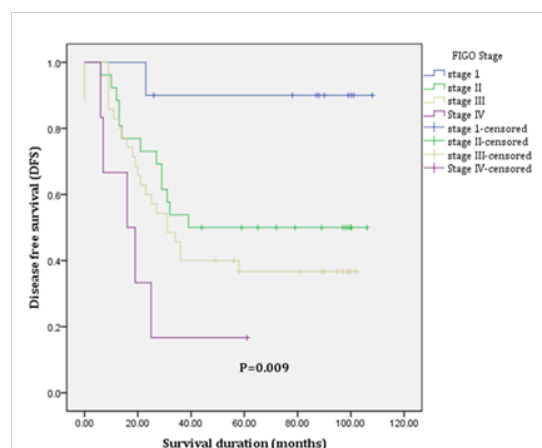**Figure 3** Kalpan- Meier analysis of overall survival per stage.

Figure 4 Kalpan-Meier analysis of disease free survival per stage.

Complications of surgery

Immediate postoperative complications among 24 patients (16 patients underwent surgery as an initial treatment and the remaining 9 patients underwent salvage surgery) included, urinary tract infection in 3 patients (12.5%) and wound infection in 4 patients (16.7%), small bowel obstruction in 2 patients (8.3%). Three patients (12.5%) developed fistula that required surgical intervention (one patient developed uretro-vaginal fistula and vesico-vaginal fistula occurred in 2 patients) all of whom underwent salvage radical hysterectomy and pelvic lymphadenectomy.

Treatment toxicity

Acute toxicity was assessed weekly during radiotherapy and the most frequent acute low grade toxicities among 61 patients received definitive chemoradiotherapy were hematological in 28 patients (45.9%), gastrointestinal in 25 patients (41.0%), nausea and vomiting in 22 patients (36.1%), skin in 15 patients (24.6%) and genitourinary in 6 patients (9.8%). Eleven patients (18.0%) developed ≥ grade 3 hematological toxicity and 5 patients (8.2%) had ≥ grade 3 gastrointestinal toxicity. As regard late toxicity (occurred after 90 days of the first day of radiotherapy), four patients (6.5%) developed ≥ grade 3 gastrointestinal toxicity and 8 patients (13.1%) developed ≥ grade 3 genitourinary toxicity.

Discussion

Majority of the patients (58%) in our study were above 40 years old. Data from cancer registries in developing countries reported the same finding; 80%-90% of women with cervical cancer in the developing countries were above the age of 40.[12] Eighty percent of women with cervical cancer in developing countries are diagnosed at advanced stages.[13] In our study, 47 patients (56.6%) presented with cervical cancer at stage III and IV, and these results were similar to other reports.[14,15] This might be attributed to the lack of screening services in our country and women tend to seek medical advice only when they have developed symptoms. In England, 23.8% of 382 women were diagnosed in stages III and IV[16] which contributes to the longer survival.[17]

Many series reported pelvic failure rate of (20%-25%) and distant failure rate of (10%-25%) after concurrent chemoradiotherapy.[18–22] Our study reported local recurrence rate of 31.2%, and distant metastasis of 20.8%. The high local recurrence rate compared to the figures of the published series might be attributed to the high percentage of advanced stage in our patients (56.6%). Another reason might be due to 15(24.6%) patients did not receive chemotherapy concurrently with radiotherapy as they were ineligible leading to poor outcome as a result of suboptimal treatment.

According to the American Cancer Society, the 5-year overall survival in the US is 72%.[17] The low 5-year OS rates (53.7%) found in our study was due to high number of cases presented with advanced disease, and treatment interruption of combined modalities which is essential for management of locally advanced disease. The reasons for treatment interruption was low hemoglobin level that required blood transfusion in order to continue chemoradiation treatment, patients received radiotherapy alone as they were ineligible for chemotherapy administration, patients travel to Cairo to receive brachytherapy course and due to crowdedness of the institution, waiting time was required for the start of brachytherapy. All these factors might contributed to high pelvic failure rate and consequently poor 5-year OS.

Radiotherapy or radical hysterectomy with bilateral pelvic lymphadenectomy for early stage cervical cancer yield comparable cure rate and survival.[23–25] Landoni et al.,[26] reported 5-year OS in stage IB-IIA of 83% and Ayhan & Tuncer[27] reported 5-year OS in stage IA, IB, IIA, and IIB of (100%, 87.9%, 71%, and 64%) respectively.[27] Two series reported that, the 5-year OS rates in stage IIIB ranged from 25-48%.[28] A survival analysis of women with cervical cancer in Brazil reported 5-year survival rates of 85% for stage I, 64.3% for stage II, 48.6% for stage III, and only 14% for stage IV.[29] In our study, 5-year OS for stage IB was 87.5%; all of whom underwent surgical resection except one. The 5-year OS in stage IIA, IIB, IIIA, IIIB, and IVA was (80%, 63.3%, 50.0%, 38.1%, and 20% respectively).

There are several prognostic factors for cervical cancer that had been reported by several studies, such as clinical stage, tumor histology, size of primary tumor, depth of invasion, tumor grade, parametrium involvement, lymph node involvement, and lymph-vascular space invasion (LVSI).[30–35] In our study, univariate analysis revealed that tumor ≥ 4cm (p= 0.033), advanced stage (p= 0.001) and patients received definitive radiotherapy alone (p= 0.034) had worse OS, while advanced clinical stage was the only statistically significant prognostic factor for DFS (0.009). Multivariate analysis showed that advanced stage was the only independent prognostic factor for poor OS and DFS; (HR= 3.237; 95% CI= 1.609 - 6.513; p= .001) and (HR= 2.694; 95% CI= 1.406 - 5.161; p= 0.003) respectively. Other risk factors were not significantly associated with poor survival; the reason might be attributed to the small number of patients enrolled in the study, which limit the power to detect any small effect of the treatment modalities adopted on the outcome.

Regarding the effect of initial treatment modalities adopted and survival, surgery and postoperative chemoradiotherapy resulted in statistically significant best 5-year OS (p= 0.034). This is probably might be due to the fact that most patients underwent radical hysterectomy and bilateral pelvic lymphadenectomy had early stage of the disease compared to patients received chemoradiotherapy or radiotherapy alone.

Conclusion

Most of cervical cancer patients were seen at an advanced disease stage which leads to poor prognosis and outcome. After analyzing the age, pretreatment hemoglobin level, histology, tumor size, lymph node metastasis, FIGO stage, histological grades and initial treatment adopted of the 77 patients with cervical cancer using Cox regression model, we found that clinical stage was independent prognostic factors for poor OS and DFS. The preventable and curable nature of the disease necessitate the establishment of an effective screening program, education of women on the benefit of early diagnosis of the disease and consequently better treatment outcome. Establishment of an effective referral system from our Institute to regional center in Cairo, and increase the facilities and services provided for the patients care and management to alleviate the crowdedness and overloading at single referral hospital which in turn reduce the waiting time between the initial phase of external beam radiotherapy and brachytherapy.

Author contributions

AM. Attia: Interpreting the data, and writing and critical revision of the article.

MA. Salem: Design and planning the research article.

G Amira: Critical revision of the article.

Conflicts of interest

The authors have no financial conflicts of interest to declare.

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