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Original Research

Survival after Intensity Modulated Radiotherapy in Stage IIIB Cancer Cervix with or without Hydronephrosis

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Background: Cervical cancer is the fourth most common cancer in women. There is lack of awareness and access to screening services in Egypt. Consequently, most cancers are diagnosed in advanced stages often with obstructive uropathy.

Methods: This prospective phase II study included 46 cervical cancer patients with stage III B (as per pre-2018 FIGO staging) presented to the Radiation Oncology Department at South Egypt Cancer Institute from January 2019 to January 2024. Patients with or without hydronephrosis. Age group between 40 and 72 years, were included. Intensity modulated radiotherapy was delivered with concurrent chemoradiation to a dose of 45 Gy in 25 fractions over 5 weeks given to whole pelvis and in case of enlarged Para aortic or retroperitoneal lymph nodes, a boost of 9 Gy was given to these enlarged nodes. Fourty one patients received intracavitary brachytherapy.

Results: The 5-year survival for patients who received radiotherapy alone was 31 % versus 86% for those who received chemoradiotherapy. The 3-year PFS was 88%. The 5- year survival was 30% versus 88% in those with and without obstructive uropathy respectively. Overall, after a mean time of 44.18+_ 7.48/44.0 (36-62) months, 76.1% of the studied patients were alive without any evidence of recurrence.

Conclusions: IMRT allows to obtain a high rate of local control and survival in cancer cervix without obstructive uropathy. To achieve optimal results, it should be chosen in selected patients.

Introduction

Cervical cancer is the second most common malignancy worldwide, with the third highest cancer mortality among female globally [1].

Obstruction and hydronephrosis is a major complication that significantly alters the overall survival in local advanced cancer cervix, Sinistrero et al where the first to investigate survival of patients after radiotherapy and conclouded that women with stage IIIB cervical cancer (17 patients) and hydronephrosis had lower 5-year survival rates compared to those without hydronephrosis (26% vs 41%) [2].

The method that is used to facilitate urinary diversion is highly dependent on physician`s preference as there is lack of recommendations concerning the management of cancer patients [3].

In loco regional advanced cancer cervix, concurrent chemo radiation with platinum- based chemotherapy followed by brachytherapy is the standard of care [4].

Intensity modulated radiotherapy (IMRT) thought to demonstrate dosimetric advantages over conventional radiotherapy in large prospective trial of local advanced cancer cervix as it showed satisfactory coverage of 98% of the target volume with decreasing gastrointestinal toxicity by 30% compared to conventional radiotherapy [5].

Meta-analysis report that definitive IMRT is equivalent to 3D radiotherapy in local advanced cancer cervix regarding disease free survival (DFS) and 3- years over all survival (OS) [6].

Aim of the work

Primary endpoints

To determine the overall survival and progression free survival in patients with local advanced cancer cervix with or without hydronephrosis after pelvic IMRT radiotherapy.

Secondary endpoints

To determine the predictive factors affecting the OS after pelvic radiotherapy.

Materials and Methods

We enrolled 46 patients in Prospective, one arm trial carried out at radiotherapy department and medical oncology department, South Egypt Cancer Institute (SECI). Between January 2019 and January 2024, the study was approved by SECI ethics committee (approval number 540) and informed written consent was taken from all patients.

Inclusion Criteria:

Histologically or cytologically confirmed adenocarcinoma or squamous carcinoma of cancer cervix. Stage IIIB cancer cervix with or without hydronephrosis.

Candidate for radiotherapy.

Written, informed consent.

Exclusion Criteria:

Early or metastatic (stage IV) cervical cancer.

Pregnancy or lactation

Contraindications to radiotherapy.

Unable or unwilling to give informed consent.

Pre-radiotherapy assessment included:

A full physical examinations, biopsy, complete blood count (CBC), liver function tests, urinalysis, chest radiography, and computed tomography (CT) or pelvic magnetic resonance imaging before

treatment.

Record baseline biochemistry, creatinine clearance and renal ultrasounds; these were repeated weekly to detect any change in renal function or degree of hydronephrosis.

Radiotherapy technique:

Patient Positioning:

Patients lied in the supine with empty bladder and empty rectum protocol. Radiopaque gold wires and markers used to locate cervix and at the distal margin of any vaginal disease.

A. Patient localization:

CT simulation for localization and determine target volumes.

B. CT scan the scan was ≤ 3 mm.

C. Target volume:

The CTV divided in to 3 groups

CTV1: gross tumor, cervix, uterus and vaginal cuff.

PTV1: CTV1+ 15 mm.

CTV2: parametriam and superior third to half of the vagina.PTV2: CTV2+ 10 mm.

CTV3: common, external, internal and presacral lymph nodes. PTV3: CTV3+ 7 mm [7].

Radiation dose and fractionation

The total dose was 45 Gy in 25 fractions, 1.8 Gy per fraction, 5 fractions per week over 5 weeks. Patients with radiologically positive Para aortic or retropretonial lymph received additional boost 9 gray to a total dose of 54 GY. Cisplatin if tolerated was given in a dose 40mg/m^2. All apart from 5 patients received intracavitery brachytherapy, the majority of them received 4x7Gy/fx.

Mode of delivery

Planning was done by IMRT, ELEKTA Monaco platform (TPS, version 6.1.2.0) and delivered by Linac Synergy platform. With 6 MV photons energy in all patients.

Dose limitation to organ at risk

Structures considered at risk include the small bowl, bladder, rectum, femoral head and the spinal cord. The dose received by these organs were kept below the standard radiotherapy dose constrains.

Statistical analysis

Data was analyzed using the Statistical Package for Social Science (SPSS), version 26.0 for Windows. Qualitative data were expressed as frequency and percentage, while quantitative data were expressed as mean ± SD or median and range according to normality of data after testing its distribution by Shapiro-Wilk test. OS was calculated from the time diagnosis to the date of death or last follow up, while PFS was the time passed between diagnosis and either death, local or distant relapse.

Survival analysis was done using a Log rank test to calculate overall survival. Univariate cox regression analysis was performed to identify prognostic factors associated with overall survival, and significant variables entered in a multivariate cox regression analysis to calculate adjusted hazardous ratio. The level of significance was considered at P value < 0.05.

Results

Patient and tumor characteristics

Clinicopathologic characteristics of 46 patients with squamous or adnocarcinoma of cancer cervix received IMRT with or without cisplatin.

The mean age of the studied patients was 55.83+-10.95 (40-72), twenty two patients had age ≥60, forty four patients had squamous cell carcinoma while 2 patients had adenocarcinoma. Twenty nine patients (63%) presented with hydronephrosis and urinary diversion was done in 30.4 % of our patients. Unilateral PCN was applied in all of them apart from 2 patients with bilateral hydronephrosis where double PCN was required. 37% of our patients received chemo radiation while 63% received radiotherapy alone, six patients diagnosed radiologically with positive para-aortic lymph-node and received 9 GY boost.as listed in Table 1.

	N=46	%
Age		
≥60	22	47.8
<60	24	52.2
Mean ± SD (range)	55.83±10.95 (40-72)	
Histology		
Squamous cell carcinoma	44	95.7
Adenocarcinoma	2	4.3
Treatment modality		
Chemoradiation	17	37
Radiotherapy	29	63
Urinary diversion		
No diversion	32	69.6
Diversion	14	30.4
Obstructive uropathy		
No obstruction	17	37
Obstruction	29	63
Radiotherapy dose		
Without boost	40	13
With boost	6	5
Outcome		
Survivors	28	60.9
Died	18	39.1
Treatment failure		

No recurrence or metastasis	30	65.2
Locaregional relapse	11	23.9
distant metastasis	5	10.9

Table 1. Characteristics of Studied Patients.

Mean time for local recurrence:44.18±7.48/ 44.0 (36.0-62.0); Mean time for metastasis:35.40±7.47/ 36.0 (24.0-45.0)

Treatment response and outcomes

The median time of follow-up calculated after the completion of radiotherapy or concurrent chemo radiation with cisplatin 40 mg/m^2 was 45 months (range 14-100 months). Thirty patients (65.2%) did not achieve local recurrence or distant metastasis. After a mean time of 44.18+_ 7.48/44.0 (36-62) months, eleven patients experienced loco-regional relapses, and five patients developed distant metastases after a mean time of 35.40+_7.47/36.0 (24-45) months, as reported in Table 1. All patients received the prescribed radiotherapy dose without interruption or comorbidity.

Survival analysis of 46 cervical cancer patients

The median overall survival (OS) was 50 months, while the median PFS was 50 months as shown in the subsequent Figures 1 and 2.

Figure 1. Kaplan Meier Curve for OS; 3- year OS is 87% 5- year OS is 50%.

Figure 2. Kaplan Meier Curve for PFS; 3- year PFS is 88%; 5- year PFS is 40%.

The OS and PFS at 3 year were 87%, 88%, respectively, and at five-year, it was 50 %, and 40% respectively. As shown in the subsequent Figures 1 and 2.

The median survival for patients that received chemoradiation was 62.00 (53.00-63.99) months, versus 47.00 (35.43-58.77) months in patients who received radiotherapy alone (p= 0.049).while the median OS in patients with non-obstructive and obstructive uropathy was 62.00 (54.77-65.22) and 47.00 (25.43-58.65) months, respectively (p=0.007), as shown in Table 2.

	Post radiation follow up	P-Value*
	Median (months), (95% CI)	Log rank test
Total overall survival	50.0 (38.84-61.15)	
Age		
≥60	47.00 (40.56-53.44)	0.638
<60	50.00 (37.14-62.85)	
Treatment modality		
Chemoradiation	62.00 (53.00-63.99)	0.049
Radiotherapy	47.00 (35.43-58.77)	
Urinary diversion		
No diversion	47.00 (37.35-56.64)	0.019
Diversion	52.33 (49.35-55.31)	
Obstructive uropathy		
No obstruction	62.00 (54.77-65.22)	0.007

Obstructive	47.00 (25.43-58.65)	
Radiotherapy dose		
Without boost	62.00 (36.70-87.29)	0.019
With boost	37.00 (29.45-44.54)	

Table 2. Overall Survival among Studied Patients' Post-radiation.

Median follow up time 45 and ranged from 14 to 100 months; 95% CI (confidence interval), *Log rank test

The 5 -year OS in patients received chemo radiation versus radiotherapy alone were 86% and 31% respectively as shown in Figure 3, while the 5- years OS in obstructive versus non obstructive uropathy patients were 30% and 88% respectively.as shown in Figure 4.

Figure 3. Kaplan Meier Curve for Type of Therapy among Studied Patients; 5-year survival for radiotherapy is 31%; 5-year survival for chemo radiotherapy is 86%.

Figure 4. Kaplan Meier Curve for Obstruction among Studied Patients; 5- year OS for non-obstructive uropathy is 88%; 5- year OS obstructive uropathy is 30%.

Significant variables for OS in univariate analysis were patients that received chemradiation, HR (95% CI) 5.89 (1.34-25.83) p=0.019, urine diversion, HR (95% CI) 7.57 (2.01-57.41) p= 0.049 non-obstructive uropathy, HR (95% CI) 4.88 (1.10-22.31) p= 0.041and, the patients did not receive radiotherapy boost, HR (95% CI) 3.32 (1.13-9.76) p=0.29.

In multivariate linear regression, the significant variables that predict better OS were the patients without hydronephrosis (non-obstruction) HR (95% CI) 16.76 (1.11-59.6) p=0.042, and those that treated with chemo radiation HR (95% CI) 8.19 (1.34-72.77) p= 0.048 (Table 3) (Figure 5).

Predictors	Univariate		Multivariate	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age	0.99 (0.95-1.03)	0.806		
Treatment modality				
Chemoradiation	Reference	0.019	Reference	0.048
RTH	5.89 (1.34-25.83)		8.19 (1.34-72.77)	
Urinary diversion				
Diversion	Reference	0.049		
No diversion	7.57 (2.01-57.41)			
Obstructive uropathy				
Non obstruction	Reference		Reference	0.042
Obstruction	4.88 (1.10-22.31)	0.041	16.76 (1.11-59.6)	
Radiotherapy dose				
Without boost	Reference	0.029		
With boost	3.32 (1.13-9.76)			

Table 3. Prognostic Factors Related to Overall Survival (OS) among Studied Patients.

Cox regression analysis; HR: hazard ratio; 95% CI: 95% confidence interval

Figure 5. IMRT Dose Distribution of 95% Coverage of Stage IIIB Cancer Cervix with Hydronephrosis.

Discussion

ASTRO cervical cancer guide line strong recommend IMRT radiotherapy in postoperative setting to decrease acute and late toxicity, in defentive radiotherapy, the strength of recommendation reduced to conditional [8, 9]. The introduction of this database revealed the answer weather the IMRT is still an option in locally advanced cancer cervix? And what is the strength of its application on survival in radiotherapy with obstructive uropathy?

IMRT versus 3D radiotherapy

Large prospective cohort study included 452 patients with local advanced cancer cervix treated with definitive chemoradiaion in two arm groups either IMRT or 3D radiotherapy, the result of study revealed significally better CSS and OS in IMRT arm compared with 3D radiotherapy arm [10].

Gandhi et al., prospective trials examined definitive treatment radiotherapy of stage IIB and IIIB cancer cervix between IMRT arm that received 50.4GY and brachytherapy ISR 10 GY and 3D arm that received 50.4 GY followed by ICR 21 GY of brachytherapy, reported no difference in disease free survival or 3- year OS between the two arms 85.7% and 76% respectively (p=0.65) comparable to results reported in our database (the 3- year OS was 87%) [11].

Yu etal., compared IMRT and 3D radiotherapy in 72 patients stage IIA-IIIB cancer cervix in dose 45 GY/22 GY and ICR 36 GY in 3D arm and 50 -51GY/22-25 fx in IMRT arm ,the result of study revealed 3- year OS of 75% and 77.8% respectively [12]. Better 3 years OS reported in our study, it can be attributed to that the majority of the studied patients 65.2% did not develop local recurrence or distant metastasis, and only 5 patients after a mean time of 35.40+-7.47/36.0(24.0-45.0) developed distant metastasis.

In line with our cohort Pracer etal., assessed the impact of IMRT in local advanced cancer cervix compared to 3 D radiotherapy in a dose 50GY/25 fx followed by vaginal brachytherapy of 12 GY/2 fx the 3 years OS was 89.2% and 82.9% respectively (p=0.44) [13]. The biological equivalent dose and comparable patient selection criteria to our study, might explain the similar survival rate.

Chemoradiation versus radiotherapy

Chemoradiotherapy is the current standard of care for local advanced carcinoma cervix patients. Haie-Meder C et al. [14], reported that addition of chemotherapy to radiation in carcinoma cervix patients improves local control and overall survival. In our analysis, there was a significant difference in survival between the two groups showing the benefit of chemotherapy in locally advanced carcinoma cervix patients. The -3 year OS was 100 % versus 66 % in chemo radiation and radiotherapy alone respectively. Chemotherapy increase the sensitization of radiotherapy in such hypoxic type of cancer, with subsequent increase the survival outcome.

Nadendla Beulah Elizabeth etal., [15] the overall survival rate for local advanced cancer cervix patients who received only RT was 24% versus 71% for those who received chemoradiotherapy (p = 0.0001). 5-year survival for patients who received RT alone was 12% versus 63% for those who received chemoradiotherapy (p = 0.0001).

In this study 5 years OS was 86 % versus 31 % in chemo radiation and radiotherapy alone respectively. This discrepancy beside disease control from radio sensitizer effect of chemotherapy, might be due to better prognostic factors in chemoradiation group as those patients had younger

age, better performance state and the majority of them were without hydronephrosis.

Impact of age on survival

In a study from India by Yeole et al. [16], which assesse impact of age and extent of disease on survival in carcinoma cervix , the 5-year relative survival rate for younger patients (<35 years) was 47.4% but decreased with increasing age. In line with other series, conducted from Thailand [17], which revealed that those above 60 years had the poorest survival, while patients aged <40 years had the best survival whereas, showing an inverse relationship of age and survival. Similar results were found in Nadendla Beulah Elizabeth etal., [15] between patients with better OS and PFS for those age less than 50 years it can be explained by associated comorbidities and poor nutritional status in elderly patients. Better survival in patients less than 60 years old was reported in this series but it lost its significance,as the median survival in patients aged less than 60 and more than 60 was 50 VS 47 months respectively(p=0.638).

Impact of hydronephrosis on survival

A study by Patel et al., [18] the presence of hydronephrosis was associated with poorer survival. Three-year OS survival rates were 37% and 74% respectively, for those with and without hydronephrosis. (p = 0.0021). Another study by Salunkhe et al., [19] showed that median OS was less than one year for patients presenting with obstructive uropathy despite urinary diversion procedures. Nadendla Beulah Elizabeth etal., study [15] the patients who received chemoradiation in local advanced cancer cervix with hydronephrosis showed significantly worse OS compared to no obstructive uropathy. The 3-year PFS was 77% versus 83% and those with and without obstructive uropathy respectively. (p = 0.0001). In our study the 5- year OS in obstructive versus non obstructive uropathy was 30% and 88% respectively. These results suggest that more disease burden, possibly poorer tumor biology and poor performance status in patients with urinary tract obstruction.

Limitation of the study

Our registry –based population approach has some limitations, first: this research concerning on survival analysis, thus other factors like tumor response or treatment related toxicity wasn’t analyzed in this research. Second, no dose modification was done in IMRT plan, lack of brachytherapy in our institute and lack of control group with small sample size might not yield accurate conclusions. Future trials with longer follow up and larger sample size is recommended.

In conclusion, the 5-year OS of stage IIIB cancer cervix, in our study were comparable to the internationally published studies. However difference is still present between centers due to variation in the representive samples. Both non obstructive uropathy and chemoradiation used as local modality stood the most powerful predictors of PFE and OS.

Declarations

Ethics approval and consent to participate.

The study was approved by SECI ethics committee and an informed written consent was taken from all patients. The committee’s reference number: 540

Consent for publication

Not applicable.

Availability of data and material

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

Competing Interests

The authors indicated no potential conflicts of interest.

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Authors' contributions

AA is the main author of the manuscript and made contributions to the protocol design. collected analyzed and interpreted the data, and drafted the manuscript.AR Provided support regarding the statistical analysis and discussion. All authors have reviewed and approved the final version of the manuscript.

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Not applicable

List of abbreviations

IMRT: intensity modulated radiotherapy, RT: radiotherapy, CRT: concurrent chemoradiation, OS: overall survival, PFS: progression free survival

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