

ORIGINAL RESEARCH

Evaluation of Effect of Radiotherapy on Response of Cervical Cancer Patients: A Multi Institutional Study

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ABSTRACT

Background: Cervical cancer is among the most frequent cancer types in women worldwide. Radiotherapy, including external beam radiation and brachytherapy, is one of the commonly used treatment options for cervical cancer. However, the response and adverse effects of radiation therapy on cervical cancer survival have been poorly investigated with inconclusive result. Therefore, the aim of this study was possibly to explore the potential factors that might affect the response to radiotherapy in patients affected with cervical cancer and thus providing information for an eminent decision making in a way to a better therapy.

Materials and Methodology: This study included 150 cases for the effective analysis. The data of the all the subject analysed were diagnosed with cervical cancer based on histopathology examination where a complete standard-protocol radiotherapy [external curative dose of 46–50 Gy (25 fractions) using Photon on LINAC with 6-10 Mega Volt energy, continued to brachytherapy using the after loading method HDR microselectron unit of ¹²⁹Ir, dose 700cGy, three times to A-point week apart].

Results: Of the total of 150 cases, 102 cases (68.29%) showed a complete response, 37 cases (24.39%) developed a partial response, seven cases (4.88%) had a stable response, and four cases (2.44%) were progressive. There were no observed gastrointestinal side effects (grade 0) for 121 cases (80.49%), 24 cases were grade 1 (16.26%), five cases were from grade 2 (3.25%), and no cases were seen grade 3.

Conclusion: Most of definitive-curative radiotherapy responses for patients with stage IIA-IIIB cervical cancer were complete (68.29%). Partial response was seen in 24.49%, stable response in 4.88% and progressive response in 2.44%. The clinical characteristics that are significantly associated with the complete response to radiotherapy was seen in

the largest tumour diameter. Clinicopathological factors like age, BMI, blood haemoglobin level, blood leucocyte count, serum albumin level, FIGO stage, histopathology and tissue differentiation were not statistically significant.

Keywords: Cervical Cancer, Radiotherapy.

INTRODUCTION

The second most common cancer affecting the women globally is reportedly the cervical carcinoma Cervix.¹ The prognosis of patients affected with cervical carcinoma is directly related to the time of diagnosis, the presence of lymph node metastases, the tumour size and the histological type where all these criteria were postulated by International Federation of Gynaecologists and Obstetricians (FIGO) stage.² Most of the cervical carcinomas are usually diagnosed at locally advanced stage.³ The associated relative 5-year survival rate for early-stage disease is mostly favourable and those observed with 92% for cervix tumours whereas the survival rates minimised to be around 56% for regional disease and 17% for distant metastasis resulted due to the cervical cancer.³ Many cases that were identified with clinically early-stage disease are managed and cured with either hysterectomy or primary radiotherapy.⁴ Various clinical studies have been conducted on the survival outcomes for patients with early-stage cervical carcinoma who had effectively undergone radical surgery or radiotherapy.⁵ But the results remain confusing and unclear. A prospective study while comparing radical hysterectomy with radiotherapy for stage I cervical carcinoma have been observed that the 10-year survival rate was reported to be around 75% with radical hysterectomy and 65% with radiotherapy.⁶ Still the noticeable difference between them was not shown to be statistically significant. Whereas in another study, the overall survival (OS) was reported to be significantly longer in patients with surgery than in those with radiation (95 vs. 70%; $p < 0.001$). Though the patients observed in both the groups had significant differences in age, tumour size and comorbid situations while the survival differences might be caused by the patient selection bias.⁷

Therefore, the aim of this study was possibly to explore the potential factors that might damage the response to radiotherapy in patients affected with cervical cancer and thus providing information for an eminent decision making in a way to a better therapy. Multivariable Cox analysis revealed striking contradictory effects of radiotherapy among the patients stratified by a single variable. Particularly the radiotherapy when combined with surgery was a potent risk factor whereas the radiotherapy alone was proved to be a beneficial factor. Radiotherapy was identified to be a risk factor in patients with TNM stage I/II based on the American Joint Committee on Cancer, whereas it was proved meritorious in patients with a tumour stage III/IV. Radiotherapy was also observed as a risk factor in younger patients (age < 45 , before menopause), whereas it was beneficial to elder patients (age ≥ 45 , menopause or latter). Additionally, radiotherapy was a risk factor in patients observed with smaller tumour size, whereas it was beneficial to patients with a large tumour size. These results inferred that the response to radiotherapy might vary based on the various clinical characteristics. Hence, the above-mentioned factors should be considered into account before performing radiotherapy to enhance the survival of patients affected with cervical cancer. These results may facilitate decision-making changes in clinical practice and might prove helpful in evaluating an appropriate treatment strategy for the management cervical cancer therapy.

MATERIALS AND METHODOLOGY

All the patients included in the study were diagnosed histopathologically to be cervical cancer. The data of all the subject were analysed based on histopathology examination where a complete standard-protocol radiotherapy [external curative dose of 46–50 Gy (25 times)

using LINAC 6-10 Mega Volt energy, continued to brachytherapy using the after loading method HDR microselectron unit of ^{129}I , dose 700cGy, three times on A-point, week apart]. Subjects were excluded if they found to have other primary tumours, or if their informational data were found to be incomplete. The protocol of this study was collected and approved by the Institutional ethical committee. This study recorded patients' pre-radiation clinical factors, such as age, BMI, blood pressure, haemoglobin level, blood leucocyte count, serum albumin, largest tumor diameter FIGO staging and pathologic characteristics (e.g., histopathology and grading). Additionally, it intends in Evaluating the radiotherapy response based on the Response Evaluation Criteria in Solid Tumors. Stata 13 was applied to evaluate the collected data further.

RESULTS

This study included 150 cases for the effective analysis. Tables 1 and 2 reveal the baseline characteristics. Of the total of 150 cases, 102 cases (68.29%) showed a complete response, 37 cases (24.39%) developed a partial response, seven cases (4.88%) had a stable response, and four cases (2.44%) were progressive. There were no observed gastrointestinal side effects (grade 0) for 121 cases (80.49%), 24 cases were grade 1 (16.26%), five cases were from grade 2 (3.25%), and no cases were seen grade 3. For genitourinary side effects, 128 cases experienced no (grade 0) side effects (85.37%), 21 cases were grade 1 (13.82%), one case was grade 2 (0.81%), and no cases were observed in grade 3. Regarding the hematologic side effects, 132 cases experienced no side effects (87.80%), 18 cases were grade 1 (12.20%), and no cases were observed in grade 2 or 3 side effects

Table 1: Clinical characteristics of patients with cervical cancer who underwent radiation treatment

Parameters	N (%)	Mean \pm SD	Median	P – value
Age (years)				
26 - 49	62 (41.46)	51 \pm 9	52 (25 - 73)	0.266
50 - 74	88 (58.54)			
BMI (kg/m²)				
<18.5	12 (8.13)	23.92 \pm 4.82	23.8 (14.2 – 46.8)	0.938
18.5 – 22.9	57 (37.40)			
>23	82 (54.48)			
Blood pressure (mmHg)				
Hypertensive	52 (34.97)	131.2 \pm 18.9	128 (91 - 188)	0.885
Non-hypertensive	98 (65.04)			
Blood Hb level				
<10	15 (9.76)	11.50 \pm 1.47	11.5 (7.4 – 15.9)	0.195
>10	135 (90.27)			
Leucocyte count (cells/mm³)				
<10,000	93 (61.79)	9585 \pm 4089	8488 (2958 - 18588)	0.972
>10,000	57 (38.21)			
Serum albumin level (g/dL)				
<3.5	29 (19.13)	3.94 \pm 0.75	4.3 (1.28 – 4.91)	0.199
>3.5	121 (80.87)			
Largest tumour diameter (mm)				
<40	55 (36.58)	45.74 \pm 18.80	42 (15 - 104)	0.036
>40	95 (63.42)			
FIGO staging				
Stage IIA	5 (3.25)	N/A	N/A	0.529
Stage IIB	51 (34.15)			
Stage IIIA	8 (5.69)			
Stage IIIB	85 (56.91)			

Table 2: Pathology characteristics of patients with cervical cancer who underwent radiation treatment

Parameters	N (%)
Histopathologic type	
Squamous cell carcinoma	109 (72.36)
Adeno-squamous carcinoma	11 (7.32)
Adenocarcinoma	29 (19.51)
Neuroendocrine	1 (0.81)
Grading of tumour	
Good	54 (35.77)
Moderate	71 (47.15)
Poor	25 (17.07)

DISCUSSION

This study had observed that most patients that were included in the study (n = 102, 68.29%) experienced a complete response. hence, the radiotherapy response appears positively good, even though it is somewhat lower than that observed in a previous study (81.6% in 38 patients in 2009, reported by the Supriana N.⁸ This difference could positively be linked to the sample size and the length of observation time. But a study by Amin et al found a similar result which showed that 70.4% with complete response, and no complete response in 29.6%.⁹ Moreover, this study also referred that some subjects had low-grade acute side effects and most of the study participants experienced no side effects. Though the side effects were observed, all the patients were able to complete the treatment course with the stipulated duration of time. The radiation side effects were reportedly much more tolerable when comparing with the chemoradiation with the same effectivity which had been followed as the treatment protocol,

In certain studies, age was taken into account as a clinical prognostic factor for local control and survival in some patients with cervical cancer. Elantholi et al observed that age more than 50 years was relatively linked with increased rates of no residual tumour.¹⁰ In this study, we observed that this result with included younger patients still cannot provide a direct relationship with lower complete response. When observed clinically, 26–50-year-old patients tends to exhibit decreased response, by 0.87 times when compared with patients who are older than 50 years. Therefore, when observed statistically, age is not a significant criterion for the complete response.

Simple nutritional status like BMI elucidated that most of our subjects were overweight to obese. This value further stands in contrast to the popular perception that advanced stage cancer patients are always malnourished and cachexic. Additionally, higher BMI in patients reported with advanced stage disease have the increased chance of mortality risk due to non-cancer related factors.¹¹ This study revealed that there is no significant relationship between BMI and complete response. When Albumin levels are taken into consideration, it showed that most of our patients were not hypo-albuminemic which clinically revealed that when albumin levels fall below 3.5 g/dL tended to decrease the response by 0.73 times but remained statistically insignificant and unnoticed. Earlier studies displayed that cancer lesion diameter with more than 4 cm were considered to be more difficult to treat when compared with the smaller size tumours because of its higher association with early onset distant metastasis.¹² Also, larger sized tumour is often associated with radioresistant cells due to high rates of mutation when compared with its counterpart.¹³ Eiffel et al researched that 1526 patients who had undergone radiation and observed that the control rate was 97% for tumours measuring less than 5 cm and 84% for tumours measuring 5–7 cm.¹⁴ Our results proved that tumour size measuring less than 40 mm was directly associated with better complete response

(2.64 times) when compared to tumours measuring more than 40 mm which revealed statistically significant results.

In this study, more than half of the subjects were reported stage IIIB disease. Many patients presented with late-stage disease which potentially posing the treatment strategy to be more difficult. Chufal et al in their study observed that most of the patients in the study group were reported with stage IIB.¹⁴ In spite of few earlier stage patients presented in our study as study participants, four patients with stage IIA disease had already undergone radiation therapy and hence irradiating them again was not considered to be ideal in our study protocol. Three patients had requested radiation treatment in lieu of surgery. One patient had undergone laparotomy but was later found to have reported with inoperable disease and opted out instead for continuing the radiotherapy. Garcia-Arias et al had observed similar findings in their study. Recently, there is a higher incidence of adenocarcinoma and lesser incidence of squamous cell carcinoma. This could be directly linked to better diagnostic classification, obesity and younger age at diagnosis.¹⁵ Reagen and Wentz postulated that adenocarcinoma was seems to be less sensitive to radiation which could lead to the poor survival. Meanwhile Fletcher et al also observed poor survival to myometrial invasion, sparing radiation in most of their treatment protocol.¹⁶ Therefore, in our study, the squamous cell carcinoma group had responded similarly to those with non-squamous cell carcinoma. Cervical cancer prognosis is also directly linked to differentiation or grading. In our study, more subjects had good and moderate differentiation and the findings were similar to what observed by Chufal et al.¹⁴ Hence, the difference in grading did not result in change in the different radiotherapy responses.

CONCLUSION

Most of definitive-curative radiotherapy responses for patients with stage IIA-IIIB cervical cancer were complete (68.29%). Partial response was seen in 24.49%, stable response in 4.88% and progressive response in 2.44%. The clinical characteristics that are significantly associated with the complete response to radiotherapy was seen in the largest tumour diameter. Clinicopathological factors like age, BMI, blood haemoglobin level, blood leucocyte count, serum albumin level, FIGO stage, histopathology and tissue differentiation were not statistically significant.

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