Original Article

Role of Histopathological Differentiation as a Prognostic Factor for Treatment Response in Locally Advanced Squamous Cell Carcinoma Cervix Patients

Abstract

Introduction: The aim of the study was to evaluate the prognostic significance of histopathological differentiation in treatment outcome of locally advanced carcinoma cervix. **Materials and Methods:** This retrospective study includes 167 patients of locally advanced carcinoma cervix treated between January 2006 and December 2008 who have received definitive chemoradiation. **Results:** The number of patients with well (85 [50.9%]) and moderately differentiated (76 [45.5%]) carcinoma was nearly equal with poorly differentiated variety having only 6 (3.6%) patients. On completion of treatment out of the 167 patients, 133 (79.6%) had a complete response and 34 (20.4%) had residual disease. On mean follow-up of 11 months, 19 (14.2%) patients had local and 5 (3.7%) had a distant relapse. Histopathological differentiation and age had no association with treatment outcome, whereas early-stage disease showed trend favoring better treatment response. **Conclusion:** Advanced stage along with poor histopathological differentiation influences the aggressiveness of the tumor responsible for distant relapse. However, histopathological differentiation has no correlation with local treatment response and overall survival. The main factor influencing the treatment outcome is the intrinsic radiosensitivity of the tumor and volume of the disease.

Keywords: *Carcinoma cervix, histopathological differentiation, intrinsic radiosensitivity, prognostic factor, treatment outcome*

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Introduction

Carcinoma cervix is the most common malignancy in women in the developing nation including India.[1] Various treatment modalities such as radiotherapy and chemoradiotherapy have been used to improve the outcome, but the results remain unsatisfactory.[2,3] The role of human papillomavirus and other risk factors in the pathogenesis of cancer cervix have been well documented, but the prognostic factors which determine the treatment outcome in these patients have been elusive.[4]

Numerous tumor and patient factors have been studied for potential prognostic value. Depth of invasion, tumor size, lymphovascular invasion, tumor hypoxia, International Federation of Gynecologists and Oncologists (FIGO) staging, treatment response, and lymph node metastasis are well-established prognostic factors.[5,6] Age, race, histopathological grading, apoptosis, and radiation response markers are other prognostic factors which are controversial.[7-9]

Squamous cell carcinoma is the most common histology seen in patients with carcinoma cervix; it is further differentiated into well-differentiated (WD), moderately differentiated (MD), and poorly differentiated (PD) depending on the degree of differentiation. Around 50%–60% of squamous cell carcinomas are MD, 30%–40% are WD, and only 5%–10% are PD. Tumor differentiation is the result of the accumulation of multiple mutations, with PD tumors having most mutations as compared to WD and MD tumors. The malignant features such as rapid tumor growth, invasiveness, and metastatic potential are more in less differentiated forms of squamous cell carcinoma; hence, less differentiated tumors represent an aggressive variety of squamous cell carcinoma as compared to more differentiated counterparts.[10]

We have undertaken this study to observe the possible impact of degree of differentiation which governs the aggressiveness of tumor on treatment response in patients of squamous cell carcinoma cervix.

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Materials and Methods

A retrospective analysis of records of patients with locally advanced nonmetastatic carcinoma cervix (Stage II and above), with squamous cell carcinoma histology, and whose differentiation was available and treated with radical radiotherapy between January 2006 and December 2008 was done. A total of 167 patients who had completed the prescribed dose were only included and treatment-defaulter patients were excluded from the study. Tumors were graded as WD, MD, and PD depending on the degree of keratin pearl formation, keratinization, and overall resemblance of carcinoma to normal squamous epithelium.[11] All patients received external beam radiotherapy, 50 Gy in 25 fractions, by 4 fields or 2 fields depending on separation, was delivered using cobalt-60 unit with 80 cm solid-state drive. All patients received weekly cisplatin 35 mg/m^2 by slow IV infusion in 2 h with appropriate hydration. Chemotherapy was stopped whenever there was persistent vomiting despite antiemetics, derangement of renal function, Grade 3 leukopenia, or in case of noncompliance.

It was followed by high dose-rate brachytherapy 18 Gy in 2–3 fractions at 1 week interval using Fletcher–Suit afterloading applicators. Those patients, who were not suitable for intracavitary radiotherapy, received supplementary radiation therapy by two lateral fields to a total dose of 66 Gy.

Patients were staged according to the FIGO staging system, after a workup, which included clinical examination, hemogram, kidney function tests, chest X-ray, intravenous pyelography, cystoscopy, and rectosigmoidoscopy. Ultrasound abdomen and computed tomography scans of abdomen were also done at the discretion of the physician.

Results

Patients' characteristics have been given in Table 1.

Age of patients ranged from 30 to 75 years with a mean value of 49.74 ± 11.19 years, 80 (47.9%) patients had Stage II and 87 (52.1%) had Stage III disease. All the patients had squamous cell histology with 85 (50.9%) having WD, 76 (45.5%) MD, and 6 (3.6%) PD histopathology.

Demographic Associations have been given in Table 2.

Majority of subjects (51.4%) aged <60 years were found to be having WD while those aged >60 years were observed to be having MD histopathology (52%), but no significant association between age and histopathological differentiation was observed ($P = 0.502$). No significant association between stage and histopathological differentiation was also observed ($P = 0.289$).

Treatment outcome has been given in Table 3.

Of the 167 patients treated, 133 (79.6%) had a complete response and 34 (20.4%) had residual disease. Nineteen

patients developed local recurrence and five patients had a distant relapse in a median follow-up of 11 months. The pattern of residual and recurrences cases is shown in the Tables 4 and 5. The distant relapse in PD group was seen in two patients out of six (33.3%) as compared with WD group which was seen in 1 out of 85 (1.17%) patients and MD group which was seen in 2 out of 76 (2.63%) which was significantly more, $P = 0.025$ (Fisher's exact test) and $P = 0.011$ (Fisher's exact test), respectively, and among patients with Stage III disease, 4 out of 87 (4.6%) developed distant relapse, whereas in Stage II, only 1 out of 80 (1.25%) had distant relapse. Local recurrence in MD group 9/76 (11.84%) and WD group 10/85 (11.75%) is similar, but local recurrence in

Table 1: Distribution of patients with respect to age, stage, and histopathological differentiation

	n (%)
Age (years)	
≤60	142 (85)
>60	25 (15)
Stage	
Stage II	80 (47.9)
Stage III	87 (52.1)
Differentiation	
Well	85 (50.9)
Moderately	76 (45.5)
Poorly	6 (3.6)

Table 2: Association of histopathological differentiation with age and stage of the patients

HPE differentiation	Age and HPE differentiation	
	≤60 years (*n*=142), *n* (%)	>60 years (*n*=25), *n* (%)
Poorly differentiated	6 (4.23)	0 (0.00)
Moderately differentiated	63 (44.37)	13 (52.00)
Well differentiated	73 (51.41)	12 (48.00)
χ^2; df; *P*	1.377; 2; 0.502	
HPE differentiation	**Stage and HPE differentiation**	
	Stage II (*n*=80), *n* (%)	Stage III (*n*=87), *n* (%)
Poorly differentiated	1 (1.25)	5 (5.75)
Moderately differentiated	38 (47.50)	38 (43.68)
Well differentiated	41 (51.25)	44 (50.57)
χ^2; df; *P*	2.483; 2; 0.289	

HPE – Histopathological examination

Table 3: Treatment outcome of the patients after receiving radical chemo-radiotherapy with median follow-up of 11 months

Outcome	Number of subjects (%)
Complete response	133 (79.6)
Residual disease	34 (20.4)
Local recurrence	19 (14.7)
Distant relapse	5 (3.75)

Table 4: Comparing the residual pattern of disease with respect to stage and histopathological differentiation

Stage	Posttreatment status	Poorly differentiated	Moderately differentiated (%)	Well differentiated (%)	Total
Stage II	No disease	1	34 (89.5)	33 (80.5)	67
	Residual	0	4 (10.5)	9 (19.5)	12
	Total	1	38	41	80
Stage III	No disease	4	28 (73.7)	33 (75.0)	61
	Residual	1	10 (26.3)	10 (25)	21
	Total	5	38	44	87

Table 5: Comparing the recurrence pattern of disease with respect to stage and histopathological differentiation

Stage	Recurrence	Poorly differentiated	Moderately differentiation	Well differentiated	Total
Stage II	Local	0	3	3	6
	Distant	0	1	0	1
Stage III	Local	0	6	7	13
	Distant	2	1	1	4
Total		2	11	11	24

Stage III disease (13/87 [14.95%]) is twice that of Stage II 6/80 (7.5%).

Treatment outcome association with age, stage, and histopathologic grading has been given in Table 6.

Treatment outcome in relation to age, stage, and histopathological examination has shown no statistically significant relation; however, Stage II patients have better treatment response as compared to Stage III patients ($P = 0.099$).

On multivariate analysis, only one subgroup of patients who are <60 years and Stage II have shown better treatment response in MD variety [Table 7].

Discussion

The value of histopathological differentiation as a prognostic factor for treatment response is controversial. Hardt *et al.*,[12] in his study observed that there was a lower incidence of complete response to radiation in keratinizing squamous cell cancers (WD) than in large cell nonkeratinizing squamous cell carcinoma, thus concluding that better differentiated forms of squamous cell carcinoma histology have poor treatment response, but no other study has found similar association. In our study, we found no association between histological differentiation and treatment response. Even studies done on head and neck squamous cell carcinoma have shown no relation between differentiation and treatment response.[13]

The relapse pattern in our study showed that distant relapse is more common in PD group as compared with that of WD and MD groups in Stage III as compared to Stage II, showing that less differentiated tumors and advanced stage are more aggressive, similar results were observed in head-and-neck squamous cell carcinoma where PD variety and advanced stage were more prone to nodal metastasis as compared to better differentiated forms.[13] Local recurrence is dependent on stage of the

Table 6: Association of treatment response with stage of the disease, histopathological differentiation, and age of patients

HPE differentiation	HPE differentiation and treatment response	
	No disease (n=133), n (%)	Residual (n=34), n (%)
Poorly differentiated	5 (83.33)	1 (16.67)
Moderately differentiated	62 (81.58)	14 (18.42)
Well differentiated	66 (77.65)	19 (22.35)
χ^2; df; *P*	0.435; 2; 0.805	
Age (years)	**Age and treatment response**	
	No disease (n=133)	Residual (n=34)
<60	114 (80.28)	28 (19.72)
>60	19 (76.00)	6 (24.00)
χ^2; df; *P*	0.240; 1; 0.624	
Stage	**Stage and treatment response**	
	No disease (n=133)	Residual (n=34)
II	68 (85)	12 (15)
III	65 (74.7)	22 (25.3)
χ^2; df; *P*	2.720; 1; 0.099	

HPE – Histopathological examination

disease (Stage III 14.95% vs. Stage II 7.5%) and not on histopathological differentiation (MD group 11.84% vs. WD 11.75%).

Histopathological differentiation influencing survival in squamous cell carcinoma in either cervix or head and neck is not established even though some studies have found some correlation.[13-15] Our study too found no correlation between differentiation and survival.

From the facts of radiobiology, it is known that radiosensitivity of squamous cell carcinoma has bell-shaped curve, which ranges from extremely radiosensitive to extremely radioresistant, so the main factor responsible for treatment response seems to be intrinsic radiosensitivity of the tumor cell.[16] *In vitro* studies have shown intrinsic

Table 7: Multivariate analysis of different subgroup of patients in relation to age, stage, and histopathological differentiation with treatment response

Age group	Histopathological differentiation		Total
	Moderately differentiated (%)	Well differentiated (%)	
Stage II			
<60 years			
No disease	30 (93.8)	27 (77.1)	57
Residual	2 (6.2)	9 (22.9)	11
Total	32	36	68
χ^2; P	3.631; 0.057		
>60 years			
No disease	4 (66.7)	6 (100)	10
Residual	2 (33.3)	0	2
Total	6	6	12
χ^2; P	2.400; 0.121		
Stage III			
<60 years			
No disease	23 (74.2)	29 (76.3)	52
Residual	8 (25.8)	8 (23.7)	16
Total	31	37	68
χ^2; P	0.041; 0.839		
>60 years			
No disease	5 (71.4)	4 (66.7)	9
Residual	2 (28.6)	2 (33.3)	4
Total	7	6	13
χ^2; P	0.034; 0.853		

radiosensitivity of cervix tumors to be independent of disease stage, tumor differentiation, and patient age. However, increased tumor radioresistance for large volume disease has been observed probably due to the presence of hypoxic region in the tumor of large volume disease.[16,17]

Patients with advanced cancer (Stage III and IVA) have poor treatment response.[12,18,19] In our study also, a trend toward a better response in Stage II as compared to Stage III was seen ($P = 0.099$), but no significant difference was seen probably because most of our Stage II patients had bulky disease (>4 cm).

Age as a prognostic factor for overall treatment outcome of carcinoma cervix is very controversial. Two European studies[7] have shown a better response in younger age whereas others have shown a better response in older patients.[12,18] Eighty-five percent of our patients were <60 years, and we found no association of age and treatment response, but on subgroup analysis patients with early stage and younger age have better treatment response in MD variety but no such correlation was seen in either WD or PD groups, which could be explained by a relatively larger sample size in <60 years group.

We observed that histopathological differentiation and age have no association with treatment response but stage and volume of the disease do influence the treatment outcome.

Intrinsic radiosensitivity of the tumor is an important factor which determines the treatment outcome. Histopathological differentiation does influence the aggressiveness of the disease with PD tumors being more aggressive than better-differentiated forms.

Conclusion

Advanced stage along with poor histopathological differentiation influences the aggressiveness of the tumor responsible for distant relapse. However, histopathological differentiation has no correlation with local treatment response and overall survival. The other factor influencing the treatment outcome is the intrinsic radiosensitivity of the tumor and volume of the disease, mainly responsible for local control. Intrinsic radiosensitivity of the tumor, which most likely governed by molecular characteristic of the tumor. This work lays the groundwork for identifying the molecular characteristics of differently differentiated tumors as predictive markers of radiation sensitivity and responsiveness.

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Conflicts of interest

There are no conflicts of interest.

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