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Original Article:

OCT4 and SOX2 as Predictive Biomarkers for Radiotherapy Efficacy among Cervical Cancer Patients of North Indian Population

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Abstract

Introduction: Cervical cancer is a leading cause of mortality among women, largely influenced by clinical and histopathological tumor characteristics at diagnosis. While tumor size is an effective predictor of chemoradiotherapy (CRT) response, variability in treatment outcomes highlights the need for reliable biomarkers. OCT4 and SOX2, key stem cell markers, have been linked to cancer progression, poor prognosis, and chemoresistance. This study aims to evaluate the expression of OCT4 and SOX2 in cervical cancer tissues and assess their potential as predictive biomarkers for radiotherapy efficacy.

Materials and Methods: The study included 56 cervical cancer patients, with detailed data on cancer stage, tumor characteristics, and treatment modalities collected from medical records. Tissue microarrays were constructed from paraffin-embedded samples, and immunohistochemical staining was performed to assess OCT4 and SOX2 expression, with staining intensity analyzed using specialized software. Histoscores were compared across subgroups, and ROC analysis determined cut-off values for biomarker expression. Kaplan-Meier survival analysis, Cox regression, and chi-square tests were used to evaluate associations between biomarker expression, survival, and disease characteristics, with statistical significance set at $p < 0.05$.

Results: The study found that 66.1% of cervical cancer patients achieved a complete response to radiotherapy, while 33.9% had a partial response. Higher SOX2 and OCT4 expression levels were significantly associated with partial response and some toxicities like diarrhea. SOX2 showed stronger predictive value for radiotherapy response compared to OCT4, with significant differences in expression between complete and partial response groups. ROC analysis highlighted SOX2 as a more reliable biomarker for predicting treatment outcomes.

Conclusion: Higher expression of SOX2 and OCT4 was significantly associated with partial response to radiotherapy in cervical cancer patients, with SOX2 showing a stronger predictive value. These biomarkers may serve as useful tools for predicting radiotherapy efficacy and guiding personalized treatment strategies.

Keywords: Cervical cancer, OCT4, SOX2, Predictive biomarkers, Radiotherapy efficacy, Immunohistochemistry, Tissue microarray, Biomarker expression

1. Introduction

Cervical cancer is a leading cause of illness and death among women worldwide, ranking as the second most common cancer in women [1]. This type of cancer arises from the abnormal growth of cells in the lining of the cervix, the lower part of the uterus [2]. The primary cause of cervical cancer is infection with high-risk types of human papillomavirus (HPV), which drives neoplastic progression primarily through the viral oncoproteins E6 and E7 [3]. Cervical cancer typically affects women between the ages of 15 and 45, with approximately 470,000 new cases and 233,000 deaths reported annually [4].The prognosis for patients with cervical cancer is largely determined by the clinical and histopathological characteristics of the tumor at the time of diagnosis. Women diagnosed at early stages of cervical cancer typically have a favorable outlook, with recurrence rates of less than 20% in stages IB-IIA. However, the risk of recurrence and metastasis rises significantly to 70% and 36%, respectively, in more advanced stages (IIB-IVB). These recurrences or metastases drastically reduce the 5-year overall survival rates, from 50-70% in stage IIB down to 40% and 10% for stages III and IV, respectively [5]. The high mortality rate associated with cervical cancer is closely linked to late-stage diagnoses, a problem especially prevalent in low-income regions where limited access to healthcare can delay the timely treatment of advanced cervical cancer cases [6].

Clinical staging, particularly tumor size, has proven to be an effective marker for predicting the response to chemoradiotherapy (CRT); however, resistance to treatment remains a significant challenge in oncologic research, especially due to its role in treatment failure [7]. Clinical evidence suggests that the effectiveness of CRT can vary greatly among cervical cancer patients, even those with similar histopathological profiles, leading to a higher risk of recurrence and metastasis [5, 8]. This variability in CRT outcomes underscores the importance of identifying new biomarkers with prognostic or predictive value, which could help tailor therapeutic strategies to the specific characteristics of both the patient and the tumor. Among cancer stem cell (CSC) markers, octamer-binding transcription factor 4 (OCT4) and sex-determining region Y-box 2 (SOX2) are transcription factors that regulate several target genes, including NANOG, Fgf4, and Utf1, as well as their own expression [5–9]. OCT4, part of the POU (Pit-Oct-Unc) family, plays a crucial role in maintaining stem cell pluripotency and guiding cell differentiation by determining the fate of embryonic stem cells [10]. In cancer, OCT4 expression in stem-like cells is linked to self-renewal and tumor development through its regulation of target genes [11]. Studies have demonstrated that OCT4 expression correlates with poor tumor differentiation, metastasis, and worse prognosis in cancers such as colon, pancreas, and lung [12–14]. SOX2, a member of the SRY-related HMG-box (SOX) transcription factor family, aids in reprogramming adult cells into induced pluripotent stem cells and sustains stem cell-like properties in cancer by interacting with other markers like NANOG and OCT4 [8]. SOX2 expression has been associated with tumor development, chemoresistance, and the maintenance of stem cell-like traits in cancer cells [15, 16].

Cancer stem cells (CSCs) and embryonic stem cells (ESCs) share key characteristics, including self-renewal, unlimited proliferation, and the ability to remain in an undifferentiated state. These traits are regulated by stem cell markers such as SOX2, NANOG, and OCT3/4, with OCT3/4 being a member of the POU domain transcription factor family [17]. Recent studies suggest that these markers are highly expressed during tumorigenesis [18], but their specific roles in promoting the development of cervical cancer remain unclear. Thus, the present study aims to evaluate the expression of OCT4 and SOX2 in cervical cancer tissues and investigate their potential as predictive biomarkers for radiotherapy response.

2. Materials and Methods

Study Design:

This was a retrospective cohort study designed to evaluate the expression of OCT4 and SOX2 as predictive biomarkers for radiotherapy efficacy in cervical cancer patients. The study focused on tissue expression analysis using immunohistochemical staining techniques to measure the levels of OCT4 and SOX2 in cervical cancer tissues. Tissue samples were collected from patients enrolled in the Pathology Department of Era's Lucknow Medical College and Hospital, Lucknow. The study also aimed to evaluate the correlation between these biomarkers and radiotherapy response and associated toxicities.

Study Participants:

A total of 56 cervical cancer patients were included in the study, with data on age, cancer stage, histopathological diagnosis, tumor grade, and lymphovascular space invasion (LVSI) extracted from medical records. The study focused on analyzing the response to radiotherapy, as well as toxicities associated with the treatment. Cervical cancer staging was performed according to the International

Federation of Gynecology and Obstetrics (FIGO) guidelines, and tumors were classified and graded based on the World Health Organization (WHO) criteria. Patients underwent surgical intervention (including radical hysterectomy with lymph node dissection) or radiation/chemoradiation therapy, depending on operability. All tissue samples and medical records were obtained with patient consent and Ethics Committee approval.

Methodology:

Tissue microarrays (TMAs) were constructed from paraffin-embedded tissues from cervical cancer cases. Four 1-mm punches were taken from representative areas of the paraffin blocks and transplanted into recipient blocks for TMA construction. Immunohistochemical (IHC) staining was performed using specific antibodies for OCT4 and SOX2. Tissue sections were deparaffinized, rehydrated, and subjected to antigen retrieval. The primary antibodies used were OCT4 (Abcam, #ab19857, 1:250) and SOX2 (Cell Signaling, #3579, 1:500). Detection was performed using the EnVision Dual Link System-HRP, followed by visualization with DAB+. The stained slides were digitized and analyzed using Digital Image Hub and TissueIA software, and the expression levels of OCT4 and SOX2 were quantified by assessing staining intensity (scored 0–3+) and overall histoscores (0–300). Negative and positive controls were included to ensure the reliability of staining.

Statistical Analysis:

The histoscores for OCT4 and SOX2 expression were compared across different patient subgroups using one-way ANOVA and independent t-tests. Receiver operating characteristic (ROC) curve analysis was used to determine the cut-off values for high expression of OCT4 and SOX2, with the goal of maximizing sensitivity and specificity. Kaplan-Meier survival analysis was conducted to evaluate the association of OCT4 and SOX2 expression with patient outcomes, including overall survival. Log-rank tests were used to compare survival curves between groups. Multivariate Cox proportional hazards regression was performed to calculate the hazard ratio for death, adjusting for potential confounding factors. Additionally, chi-square tests were used to assess the association between OCT4 and SOX2 expression levels and disease characteristics. All statistical analyses were performed using SPSS version 21.0, with a p-value of less than 0.05 considered statistically significant.

3. Results

Table 1. Baseline Characteristics of Cervical Cancer Cases

Baseline Characteristics		No.	%
Age	25 - 34 yr	11	19.6%
	35 - 44 yr	15	26.8%
	45 - 54 yr	20	35.7%
	55 - 65 yr	10	17.9%
stage	Ib	0	0.0%
	IIa	1	1.8%
	IIb	13	23.2%
	IIIb	42	75.0%
Histopath Diagnosis	Keratinizing squamous cell Ca	42	75.0%
	Non Keratinizing squamous cell Ca	14	25.0%
Histopath grade	Well differentiated	12	21.4%
	Moderately differentiated	28	50.0%
	Poorly differentiated	16	28.6%

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Baseline characteristics of cervical cancer cases revealed that the majority of patients (35.7%) were aged between 45 and 54 years, followed by 26.8% in the 35 to 44-year age group. A smaller percentage, 19.6%, were between 25 and 34 years old, while 17.9% were aged between 55 and 65 years.

Regarding the cancer stage, the majority of cases (75.0%) were diagnosed at stage IIIb, while 23.2% were at stage IIb. A very small proportion (1.8%) were at stage IIa, and there were no cases at stage Ib.

Histopathological diagnosis showed that 75.0% of cases were keratinizing squamous cell carcinoma, and 25.0% were non-keratinizing squamous cell carcinoma. In terms of histopathological grade, 50.0% of cases were moderately differentiated, 28.6% were poorly differentiated, and 21.4% were well differentiated.

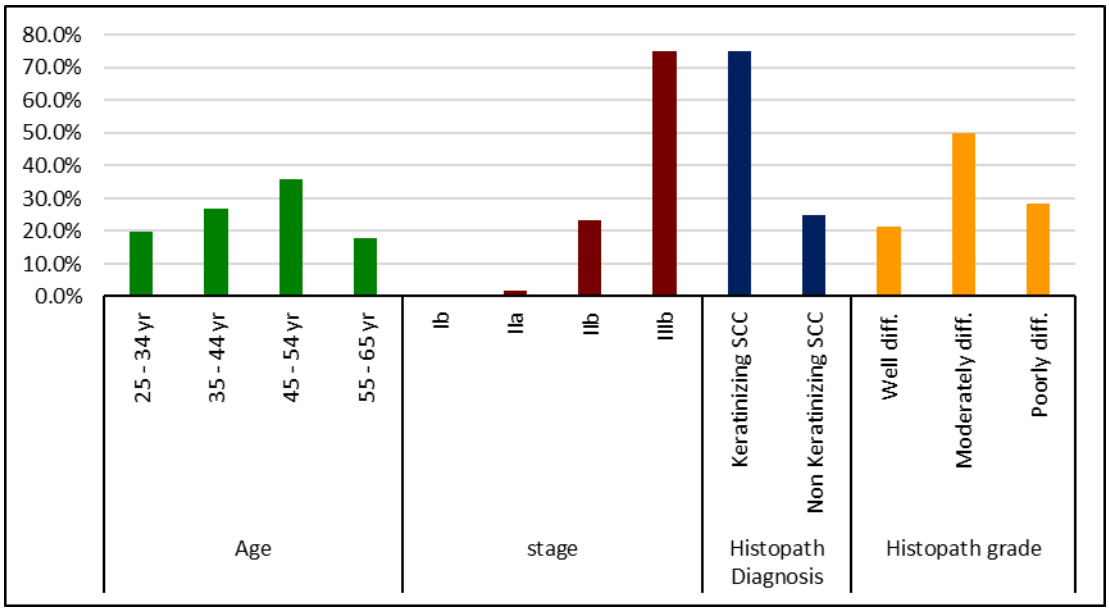


Table 2. Response of Radiotherapy

Response of Radiotherapy	No.	%
Complete (CR)	37	66.1%
Partial (PR)	19	33.9%

The response to radiotherapy among the patients showed that 66.1% achieved complete response (CR), while 33.9% exhibited a partial response (PR). This indicates that a significant majority of patients experienced full remission following treatment.

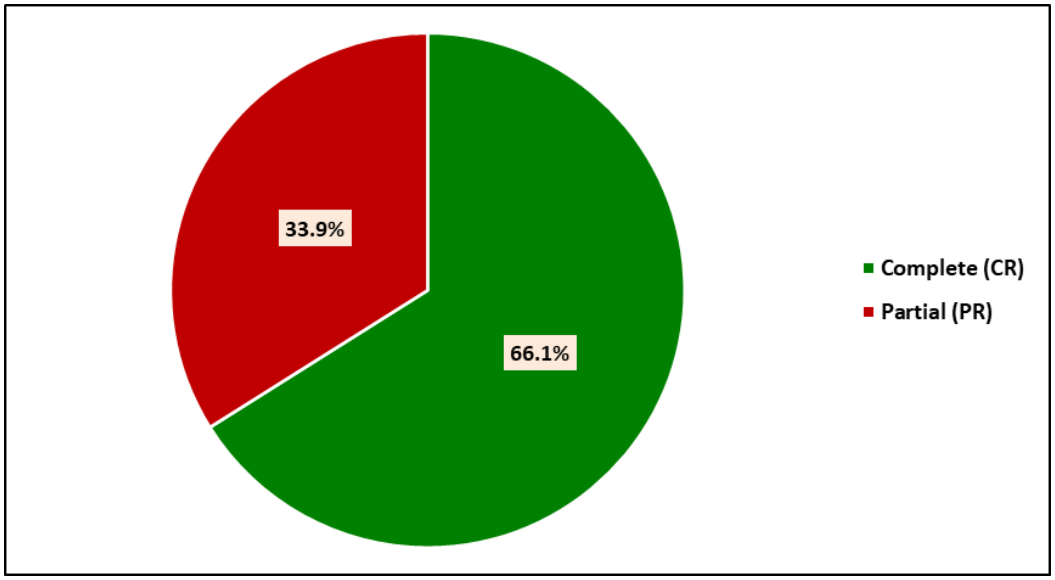


Table 3. Distribution of Radiotherapy Toxicities

Toxicities	No.	%
Skin - moist disquamation	0	0.0%
Ulceration	1	1.8%
Confluent mucositis	5	8.9%
Diarrhoea	19	33.9%
Enteritis/Proctitis	10	17.9%
Genitourinary - cystitis	1	1.8%

The reported toxicities from treatment included diarrhea in 33.9% of patients, enteritis/proctitis in 17.9%, and confluent mucositis in 8.9%. Less common side effects included ulceration and genitourinary cystitis, each affecting 1.8% of patients. There were no cases of skin moist desquamation recorded.

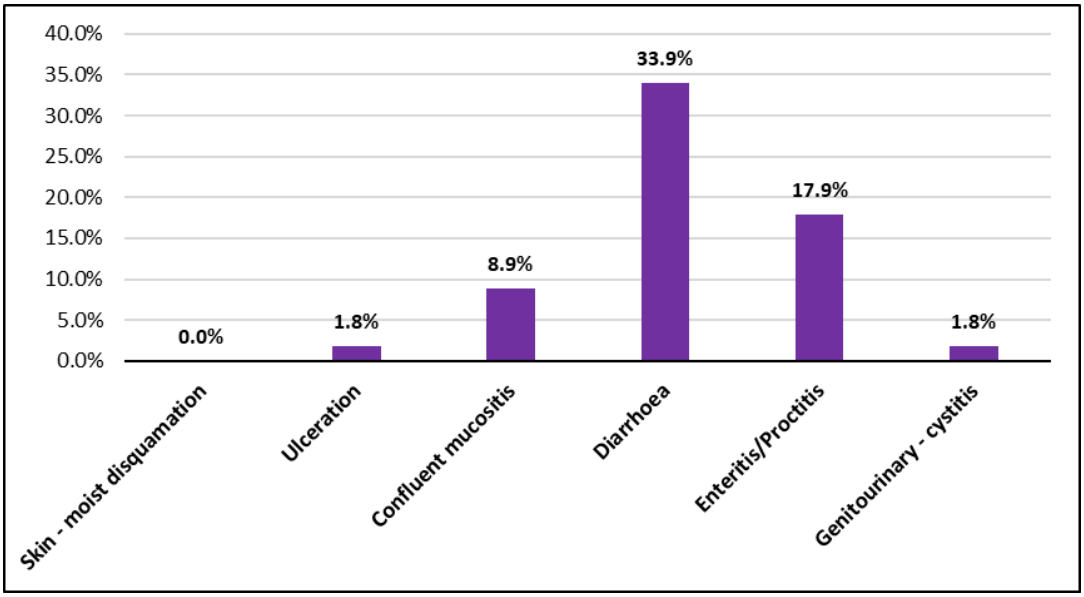


Table 4. Correlation of OCT4 & SOX2 Expressions with Disease Characteristics

Disease Characteristics		Transcription factors			
		SOX2 Expression score		OCT4 Expression score	
		Mean	SD	Mean	SD
Stage	IIa	4.00		3.00	
	IIb	4.54	3.18	5.31	3.52
	IIIb	5.38	3.03	5.93	3.16
	Kruskal Wallis test	chi sq=1.10, p=0.577		chi sq=1.46, p=0.482	
Histopath Diagnosis	Keratinizing squamous cell Ca	4.81	2.90	5.14	2.84
	Non Keratinizing squamous cell Ca	6.21	3.29	7.50	3.72
	Mann Whitney test	z=1.41, p=0.159		z=2.13, **p=0.034**	
Histopath grade	Well differentiated	4.92	2.84	5.25	3.41
	Moderately differentiated	5.50	3.33	6.36	3.28
	Poorly differentiated	4.75	2.72	5.00	2.92
	Kruskal Wallis test	chi sq=0.30, p=0.860		chi sq=2.27, p=0.321	

The disease characteristics based on transcription factor expression revealed that SOX2 and OCT4 expression scores varied across stages and histopathological categories. For stage IIa, the mean SOX2 expression score was 4.00, while OCT4 was 3.00. Stage IIb had mean SOX2 and OCT4 scores of 4.54 and 5.31, respectively, and stage IIIb showed higher mean scores of 5.38 for SOX2 and 5.93 for OCT4. However, the Kruskal-Wallis test did not show statistical significance for either SOX2 (chi sq=1.10, p=0.577) or OCT4 (chi sq=1.46, p=0.482) across stages.

In terms of histopathological diagnosis, keratinizing squamous cell carcinoma had mean SOX2 and OCT4 expression scores of 4.81 and 5.14, while non-keratinizing squamous cell carcinoma showed higher scores of 6.21 for SOX2 and 7.50 for OCT4. The Mann-Whitney test demonstrated no significant difference for SOX2 (z=1.41, p=0.159), but a significant difference was found for OCT4 (z=2.13, p=0.034).

Regarding histopathological grades, the mean SOX2 expression score for well-differentiated carcinoma was 4.92, moderately differentiated carcinoma had a mean of 5.50, and poorly differentiated carcinoma had a mean of 4.75. For OCT4, well-differentiated, moderately differentiated, and poorly differentiated carcinomas had mean scores of 5.25, 6.36, and 5.00, respectively. The Kruskal-Wallis test showed no significant differences for SOX2 (chi sq=0.30, p=0.860) or OCT4 (chi sq=2.27, p=0.321) across histopathological grades.

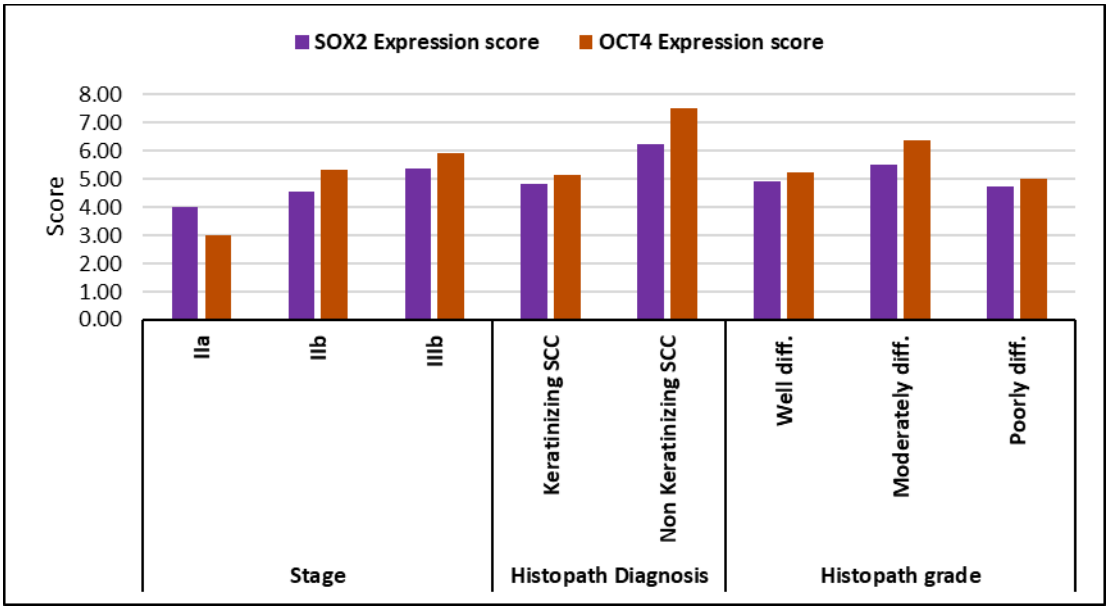


Table 5. Correlation of OCT4 & SOX2 Expressions with Radiotherapy Response

Response	Transcription factors			
	SOX2 Expression score		OCT4 Expression score	
	Mean	SD	Mean	SD
CR	3.76	2.29	4.95	2.95
PR	7.89	2.38	7.26	3.23
Mann Whitney test	z=4.76, **p<0.001**		z=2.40, **p=0.016**	

The response to treatment, based on transcription factor expression, showed distinct differences between complete response (CR) and partial response (PR) groups. For patients with CR, the mean SOX2 expression score was 3.76 with a standard deviation (SD) of 2.29, while the mean OCT4 expression score was 4.95 with an SD of 2.95. In contrast, patients with PR had significantly higher mean SOX2 and OCT4 expression scores of 7.89 (SD 2.38) and 7.26 (SD 3.23), respectively. The Mann-Whitney test revealed a highly significant difference in SOX2 expression ($z=4.76$, $p<0.001$) and a significant difference in OCT4 expression ($z=2.40$, $p=0.016$) between the two response groups.



Table 6. Correlation of OCT4 & SOX2 Expressions with Radiotherapy Toxicities

Toxicities		Transcription factors			
		SOX2 Expression score		OCT4 Expression score	
		Mean	SD	Mean	SD
Skin - moist disquamation	No	5.16	3.03	5.73	3.22
	Yes	-	-	-	-
	Mann Whitney test	NA		NA	
Ulceration	No	5.11	3.03	5.73	3.25
	Yes	8.00		6.00	
	Mann Whitney test	z=0.85, p=0.398		z=0.25, p=0.801	
Confluent mucositis	No	5.10	3.12	5.75	3.31
	Yes	5.80	2.05	5.60	2.30
	Mann Whitney test	z=0.83, p=0.407		z=0.06, p=0.953	
Diarrhoea	No	4.51	2.69	5.16	3.15
	Yes	6.42	3.32	6.84	3.13

	Mann Whitney test	z=1.97, p=0.049		z=1.93, p=0.054	
Enteritis/Proctitis	No	5.09	3.13	5.61	3.26
	Yes	5.50	2.64	6.30	3.09
	Mann Whitney test	z=0.51, p=0.611		z=0.76, p=0.447	
Genitourinary - cystitis	No	5.15	3.06	5.67	3.21
	Yes	6.00		9.00	
	Mann Whitney test	z=0.41, p=0.684		z=1.10, p=0.271	

The correlation between OCT4 and SOX2 expression scores and radiotherapy toxicities was analyzed to explore potential associations. For skin moist desquamation, no analysis was performed as no cases were reported. In the case of ulceration, the mean SOX2 expression score for those without ulceration was 5.11 (SD 3.03), while the score for those with ulceration was 8.00. The Mann-Whitney test showed no significant difference (z=0.85, p=0.398). Similarly, the OCT4 expression scores were 5.73 (SD 3.25) for those without ulceration and 6.00 for those with ulceration, with no significant difference (z=0.25, p=0.801).

For confluent mucositis, the SOX2 expression score was 5.10 (SD 3.12) for those without the condition and 5.80 (SD 2.05) for those with it, with no significant difference (z=0.83, p=0.407). The OCT4 expression score for those without confluent mucositis was 5.75 (SD 3.31), and for those with it, 5.60 (SD 2.30), also showing no significant difference (z=0.06, p=0.953).

In cases of diarrhea, patients without this toxicity had a mean SOX2 expression score of 4.51 (SD 2.69), while those with diarrhea had a higher score of 6.42 (SD 3.32), showing a statistically significant difference (z=1.97, p=0.049). The OCT4 expression score was similarly higher in patients with diarrhea (6.84, SD 3.13) compared to those without it (5.16, SD 3.15), with a marginally non-significant difference (z=1.93, p=0.054).

For enteritis/proctitis, the SOX2 expression score for those without the condition was 5.09 (SD 3.13) and 5.50 (SD 2.64) for those with it, with no significant difference (z=0.51, p=0.611). The OCT4 scores were 5.61 (SD 3.26) and 6.30 (SD 3.09) respectively, also showing no significant difference (z=0.76, p=0.447).

Lastly, for genitourinary cystitis, the SOX2 expression score was 5.15 (SD 3.06) for those without cystitis and 6.00 for the single patient with cystitis, with no significant difference (z=0.41, p=0.684). The OCT4 score was 5.67 (SD 3.21) for those without cystitis and 9.00 for the patient with cystitis, with no significant difference (z=1.10, p=0.271).

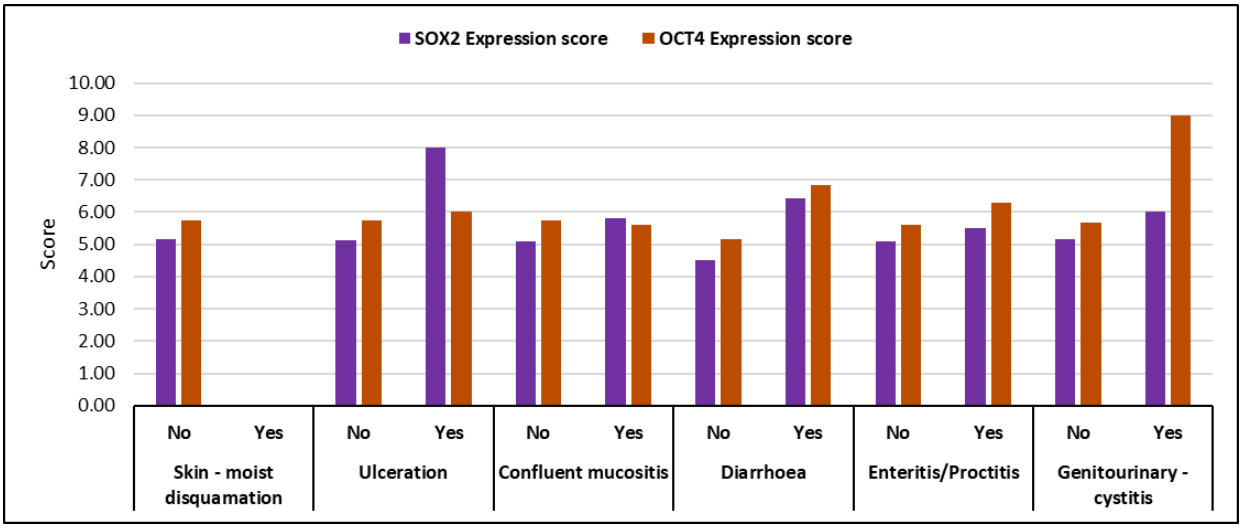


Table 7. Logistic Regression Analysis to Establish OCT4 & SOX2 Expressions combinedly as Predictive Markers for Radiotherapy Response

Dependent : Radiotherapy Response	B	S.E.	p-value	Exp(B)/OR	95% C.I.for EXP(B)/OR	
					Lower	Upper
SOX2	0.730	0.21	0.001	2.07	1.37	3.14
OCT4	-0.114	0.15	0.461	0.89	0.66	1.21
Constant	-4.176	1.10	0.000	0.02		
Inherent Validity	80.4%					

A logistic regression analysis was conducted to evaluate the combined predictive potential of SOX2 and OCT4 expression levels as markers for radiotherapy response. The dependent variable was radiotherapy response (complete vs partial).

For SOX2 expression, the regression coefficient (B) was 0.73 with a standard error (SE) of 0.21, yielding a statistically significant p-value of 0.001. The odds ratio (OR) for SOX2 was 2.07, with a 95% confidence interval (CI) ranging from 1.37 to 3.14, indicating that higher SOX2 expression significantly increases the likelihood of a complete radiotherapy response.

In contrast, the OCT4 expression coefficient (B) was -0.11 with an SE of 0.15, and the p-value was 0.461, showing no significant association between OCT4 expression and radiotherapy response. The odds ratio for OCT4 was 0.89 (95% CI: 0.66–1.21), suggesting no meaningful impact of OCT4 on the treatment outcome.

The constant in the model had a coefficient of -4.18 (SE = 1.10, $p < 0.001$), with an overall model accuracy or inherent validity of 80.4%, indicating that the model correctly predicted radiotherapy response in a substantial proportion of cases. The combined expression levels of SOX2 and OCT4 highlight SOX2 as a significant predictive factor for radiotherapy response.

The above analysis formed the following equation of prediction for complete response:

$R = 0.730(SOX2) – 0.114(OCT4) – 4.176$

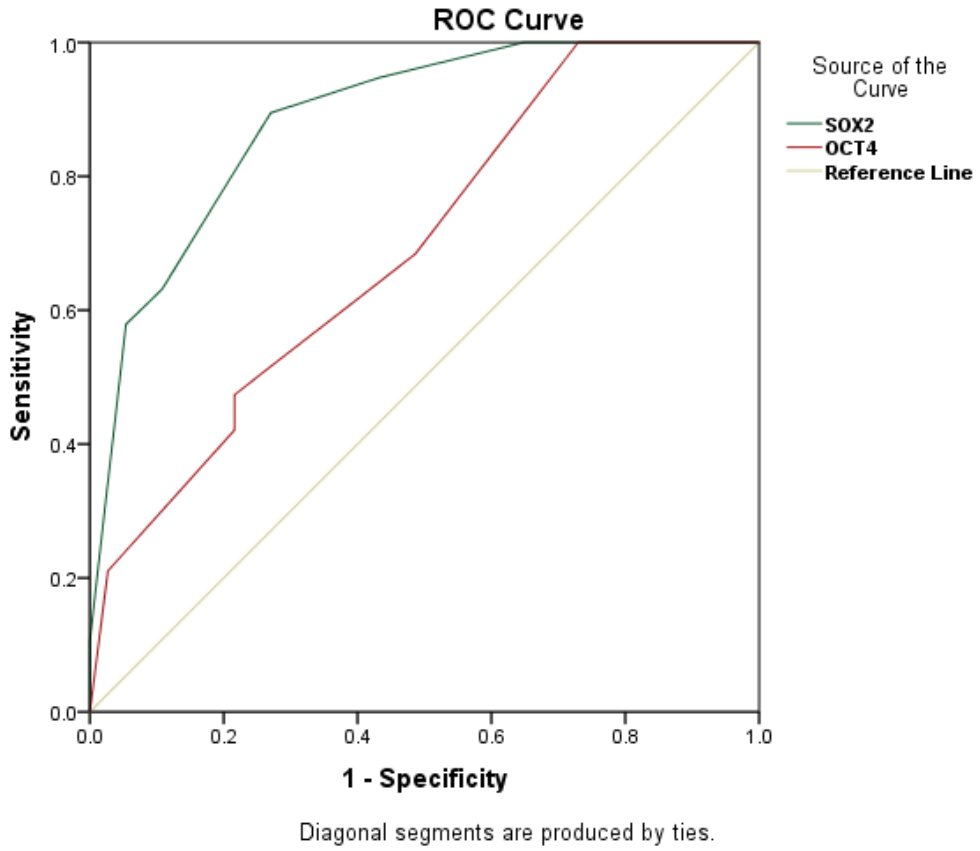
Complete response is predicted if $R > 0$ for values of SOX2 and OCT4

Table 8. ROC Analysis to Estimate Optimum Cut Offs of OCT4 & SOX2 Expressions to Predict Radiotherapy Response

Parameter	SOX2	OCT4
AUROC (95% CI)	0.886 (0.799-0.973)	0.694 (0.553-0.835)
optimum cut off for PR	OCT4>=5.0	SOX2>2.5
Sensitivity	89.5 (82.1-97.9)	100 (100-100)
Specificity	73.0 (61.4-84.6)	27.0 (15.4-38.6)

ROC analysis was conducted to determine the optimum cut-off values for SOX2 and OCT4 expressions in predicting radiotherapy response. The Area Under the ROC Curve (AUROC) for SOX2 was 0.886, with a 95% confidence interval (CI) of 0.799 to 0.973, indicating excellent predictive ability for radiotherapy response. The optimal cut-off value for partial response (PR) was identified as SOX2 > 2.5, which yielded a high sensitivity of 89.5% (95% CI: 82.1–97.9%) and a specificity of 73.0% (95% CI: 61.4–84.6%).

In contrast, the AUROC for OCT4 was 0.694 (95% CI: 0.553–0.835), reflecting moderate discriminatory power. The optimal cut-off for predicting PR was identified as OCT4 ≥ 5.0, with a sensitivity of 100% and a much lower specificity of 27.0% (95% CI: 15.4–38.6%). This suggests that while OCT4 has excellent sensitivity, it may result in a higher rate of false positives compared to SOX2.



4. Discussion

The findings of our study are consistent with those of previous research in terms of patient demographics, cancer staging, histopathology, and treatment outcomes. Similar to studies by Paul SB et al., Shantla S et al., Spartacus RK et al., and Devi S et al., the majority of cervical cancer patients were aged between 45 and 54 years, which is comparable to the 41-50-year age range highlighted in those studies [19-22]. However, we noted a slightly higher prevalence in the 35-44-year group compared to some of these reports, where the second most affected group was 51-60 years.

Our results also align with those of Wadhvani R et al., Kaverappa et al., and Singh R et al., who reported that most cervical cancer cases were diagnosed at an advanced stage (IIB, III, IV) [23-25]. In our study, 75.0% of patients were diagnosed at stage IIIb, further supporting these findings. Both our study and those reported by Akhthar PS et al [26]. and Narayanswamy N et al [27]. showed that squamous cell carcinoma was the predominant histopathological type, which was true in 75.0% of cases in our analysis.

Additionally, our observation that 66.1% of patients achieved a complete response (CR) to radiotherapy supports findings from studies indicating chemoradiation as the most effective treatment modality. The correlation of advanced disease stage with increased lymph node metastasis, as reported by Akhtar PS et al. and Narayanswamy N et al., was also reflected in our data, where higher SOX2 and OCT4 expression scores were observed in patients with advanced-stage disease.[26, 27].

Our study found that SOX2 and OCT4 expression levels varied based on cancer stage and histopathological categories, and that these biomarkers were significantly associated with radiotherapy outcomes, particularly in predicting complete versus partial responses. When comparing our findings with other studies, we find both supporting evidence and some differing results.

Several studies have reported findings similar to ours regarding the role of SOX2 and OCT4 in cancer progression and response to therapy. For example, studies by Chiou SH et al. and Singh S et al [16, 28] demonstrated that SOX2 and OCT4 are critical in maintaining stem cell-like properties in cancer cells, contributing to tumor aggressiveness and treatment resistance. This is similar to our observation where higher expression of SOX2 and OCT4 was associated with partial response (PR) to radiotherapy. Their research also highlighted that higher levels of these markers correlate with poorer prognosis. This observation also aligns with our findings where patients with higher SOX2 and OCT4 expression had a lower chance of complete response (CR).

Similarly, a study by Rodda DJ et al [29] found that the interaction of SOX2 and OCT4 regulates the expression of downstream targets critical for maintaining pluripotency and cancer stemness, which supports the idea that elevated expression of these factors contributes to treatment resistance, as observed in our study. Additionally, Ponti D et al [15] showed that SOX2 and OCT4 are overexpressed in various cancers, where they promote the self-renewal of cancer stem cells (CSCs), further highlighting their role in cancer progression and resistance to therapy .

Furthermore, in lung and breast cancers, SOX2 expression has been associated with chemoresistance and tumor survival, as reported by Takahashi K and Yamanaka S [30] Their research aligns with our findings that SOX2 is a stronger predictor of treatment response than OCT4. The fact that SOX2 had a higher area under the ROC curve (AUROC) in our study suggests that it might have a broader role across different cancer types as a reliable predictor of treatment outcomes, a conclusion supported by other research in solid tumors like colorectal and pancreatic cancers.

In contrast, other studies have placed more emphasis on OCT4 as the key regulator of cancer stem cell (CSC) properties and therapy resistance. For instance, Wen J et al. and Meng HM et al [31, 32] found that OCT4 was highly correlated with tumor progression, metastasis, and poor prognosis in pancreatic and colorectal cancers. These studies suggest that OCT4 may play a more prominent role in other cancer types than what we observed in cervical cancer, where SOX2 appeared to have a more significant impact on radiotherapy outcomes. This discrepancy could be attributed to cancer-specific variations in CSC marker expression and the microenvironmental context of different tumors.

Several other studies, such as those by Swamy MN et al. and Wadhwani R et al [33, 34], further support the notion that squamous cell carcinomas with high expression of stem cell markers like SOX2 and OCT4 tend to exhibit aggressive behavior and resistance to conventional treatments like radiotherapy. These studies highlight that the overexpression of CSC markers not only promotes tumor growth but also reduces the effectiveness of therapies, thus aligning with our findings that partial responders had higher expression of both SOX2 and OCT4.

In terms of treatment toxicity, our study's observation of the correlation between higher SOX2 and OCT4 expression and diarrhea during radiotherapy is relatively novel. Most prior studies have not extensively explored the relationship between biomarker expression and treatment-related toxicities. Studies like those of Ameen NS et al. and Akhtar PS et al [35, 36] focused more on treatment outcomes and response but did not examine these correlations with specific radiotherapy side effects. Thus, this aspect of our research presents new insights that require further investigation to determine the potential mechanisms by which SOX2 and OCT4 might contribute to these side effects.

Overall, our findings are largely supported by existing literature regarding the role of SOX2 and OCT4 in tumor progression, chemoresistance, and treatment response. However, there are some variations in the relative importance of SOX2 and OCT4 across different cancer types, with SOX2 emerging as a more reliable predictor of radiotherapy response in our cervical cancer cohort. Further studies are needed to clarify the role of these biomarkers in different cancers and to explore their association with treatment-related toxicities. Additionally, ongoing research into the CSC biology of different cancer types could provide more nuanced insights into the roles of SOX2 and OCT4 in therapeutic resistance across various oncological contexts.

5. Conclusion

The study found that higher expression levels of SOX2 and OCT4 were significantly associated with partial response to radiotherapy in cervical cancer patients, with SOX2 emerging as a stronger predictive biomarker. These findings suggest that evaluating SOX2 and OCT4 expression could help identify patients more likely to benefit from radiotherapy, thus guiding personalized treatment strategies. However, the study is limited by its relatively small sample size and retrospective nature, which may affect the generalizability of the results. Further validation in larger, prospective cohorts is necessary to confirm the clinical utility of these biomarkers.

Ethical Considerations

Compliance with ethical guidelines

This article is a review with no human or animal sample.

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Author's contributions

The authors equally contributed to preparing this article.

Conflict of interest

The authors declare no conflict of interest.

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