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Research Article

Non Squamous Histology in Cervical Cancer: Prognostic Insights from Institutional Study

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Abstract

Background: *Non-squamous histologies in carcinoma cervix, including adenocarcinoma (AC) and adenosquamous carcinoma (ASC), represent a clinically and biologically distinct subgroup with reportedly inferior outcomes compared to squamous cell carcinoma (SCC). Limited data exist regarding their treatment outcomes in the Indian population. This study aimed to evaluate the clinical profile, treatment response, patterns of failure, and survival outcomes in patients with non-squamous carcinoma of the cervix treated at our tertiary care center.*

Methods: *This retrospective study included patients with histologically confirmed non-squamous cervical cancer treated with definitive or adjuvant radiotherapy between January 2020 and December 2024. Clinical characteristic, pathological, and treatment details were collected. Disease-free survival (DFS), overall survival (OS), and patterns of failure were analyzed. Statistical analysis was performed using the unpaired t-test.*

Results: *A total of 34 patients were included, with a mean age of 48.6 years. Adenocarcinoma was the most common histology (21 patients ,61.8%), followed by adenosquamous carcinoma in 7 (20.6%) and other rare subtypes (6 patients,17.6%). The most common stage at the presentation was FIGO IIB. Twelve patients (35.3%) underwent primary surgery followed by adjuvant therapy, and 22 (64.7%) received definitive concurrent chemoradiation (CCRT).*
After a median follow-up of 28 months, the mean DFS and OS were 27.2 and 29 months, respectively. Patients undergoing surgery had numerically higher DFS and OS (30.4 and 34.3 months) compared to those receiving definitive CCRT (25.5 and 26.1 months), though not statistically significant ($p = 0.63$ for DFS; $p = 0.34$ for OS). Failure patterns showed slightly higher recurrence in the surgery group (5 patients, 41.6%) compared to the CCRT group (3 patients, 13.6%).

Conclusion: *Non-squamous cervical cancers exhibit relatively poorer outcomes and distinct failure patterns. While primary surgery may offer a survival advantage in early-stage disease, CCRT remains the mainstay for advanced stages. Tailored treatment approaches and molecular profiling are warranted to optimize outcomes in this high-risk subgroup.*

Key words: *Cervical cancer, adenocarcinoma, adenosquamous carcinoma, chemoradiation, surgery, survival, recurrence pattern, non-squamous histology.*

Introduction

Cervical cancer remains a major global health burden, ranking as the fourth most common cancer among women worldwide. According to GLOBOCON 2022, there were appropriately 662301 new cases and 348874 deaths globally, with a significant proportion in low- and middle- income countries [1]. In India, cervical cancer continues to be the second most common cancer among women, with approximately 127526 new cases and 79906 deaths [2].

Histologically, squamous cell carcinoma (SCC) is the predominant subtype, accounting for appropriately 80% of cases globally, while adenocarcinoma (AC) and adenosquamous comprises around 15-20%[3]. In India, the distribution slightly differs, with squamous histology accounting for approximately 89.5% of cervical cancer, adenocarcinoma for 6-7%, and adenosquamous carcinoma for about 1%[4]. Although relatively uncommon, the incidence of adenocarcinoma is rising, particularly in younger women, due to its association with high-risk HPV type 18 and limited cytology based screening programs.

Non squamous histologies, including adenocarcinoma and adenosquamous carcinoma, exhibit distinct clinical and biological characteristics compared to SCC. They are often considered less radiosensitive, have a higher likelihood of presenting at an advanced stage, and greater tendency for distant metastases, particularly lungs and para aortic lymph nodes [5,6]. Studies have reported inferior local control, disease-free survival (DFS), and overall survival (OS) for adenocarcinoma compared to SCC, even with standard concurrent chemo radiation (CCRT) protocols[7]. However, treatment strategies for non-squamous histologies remain controversial, with some experts advocating for primary surgery or intensified systemic therapy in selected cases.

Indian data on non-squamous cervical cancers are sparse, as most studies primarily focus on SCC. Some retrospective studies suggest that adenocarcinoma and adenosquamous carcinoma have worse outcomes and a distinct recurrence pattern. Given these challenges, our study aims to analyze the clinical profile, treatment response, patterns of failure, and survival outcomes in patients with non-squamous carcinoma of the cervix treated at our institution.

Material and Methods

Study design

This is a retrospective observational study conducted at the Department of Radiation Oncology , our institute, a tertiary care centre in India. The study was approved by the institutional Ethics Committee.

All patients diagnosed with carcinoma cervix with non-squamous histology who received definitive or adjuvant radiotherapy between 2020- 2024 were included in the analysis. Patients with histology of squamous

cell carcinoma were excluded.

Data collection

Clinical and treatment details were collected from hospital medical records and radiotherapy department registry. Demographics , clinical presentation, histopathology, treatment details (surgery details, type of radiation- radical or adjuvant, EBRT techniques & dose, concurrent chemotherapy, brachytherapy) and follow up data i.e. details of recurrence (site and time), disease status, survival outcome.

Treatment Protocol

Patients with early-stage who were operable underwent radical hysterectomy with pelvic lymph node dissection. Surgical histopathology was reviewed for risk factors including tumour size, deep stromal invasion, positive margins, parametrial involvement, lymphovascular space invasion (LVSI), and lymph node status. Patients with high-risk or intermediate-risk features post surgery received adjuvant external beam radiotherapy (EBRT) with or without concurrent chemotherapy (CCRT). Definitive CCRT is received by patients who were unsuitable for surgery or with locally advanced disease.

All patients underwent pelvic EBRT to a dose of 45-50.4 Gy in 25-28 fractions, using either 3D conformal radiotherapy (3DCRT) or intensity modulated radiotherapy (IMRT). Concurrent chemotherapy with weekly Cisplatin (40mg/m2) was given to eligible patients with adequate renal function and hematological parameters. High-dose rate intracavitary brachytherapy (ICRT) was administered in 3 fractions, totally ~21Gy, prescribing to point A.

Follow-up protocol and Outcome Assessment

Patients were followed up every 3 months for the first 2 years,every 6 months for the next 3 years, and annually thereafter, or until disease recurrence or death. Follow-up assessments included clinical examination, imaging (ultrasound/CT/MRI as appropriate) when indicated. Outcomes measured included, DFS i.e. Time from treatment completion to recurrence or last follow-up, OS i.e. Time from diagnosis to death from any cause or last follow-up and Pattern of failure - Local, regional, or distant recurrence.

Results

A total of 34 patients with non-squamous histology of carcinoma cervix were treated at our institution between January 2020 and December 2024. The mean age at presentation was 48.6 years (33-70 years), with the majority of patients (14) falling in the 41-50-year age group, followed by those aged 31-40 (8) and 51-60 years (8). The most common stage at presentation was FIGO stage IIB (13, 38.2%), followed by IIIC1 (8, 23.5%).

Among the histological subtypes, adenocarcinoma was most frequent, seen in 21 patients (61.8%), followed by adenosquamous carcinoma in 7 patients (20.6%). Rare subtypes (17.6%) included adenocarcinoma with neuroendocrine differentiation (1 patient, 2.9%), papillary serous type adenocarcinoma (1, 2.9%), neuroendocrine carcinoma (1, 2.9%), papillary squamotransitional carcinoma (1, 2.9%), squamotransitional carcinoma (1, 2.9%), and leiomyosarcoma (1, 2.9%). Twelve patients (35.3%) underwent primary surgery followed by adjuvant therapy, while the remaining 22 (64.7%) received definitive CCRT (Table 1).

After a median follow-up of 28 months, the overall mean DFS for the entire cohort was 27.2 months, and the mean OS was 29 months. In the surgical subgroup, the mean DFS and OS were 30.4 and 34.3 months, respectively. Five patients in this group developed disease recurrence, with a mean time to local relapse of 7.3 months and distant failure at 5.7 months. The mean OS for those who failed in the surgical subgroup was 14.6 months. Among patients treated with definitive CCRT, the mean DFS and OS were 25.5 months and 26.1 months, respectively (Table 2). Three patients experienced recurrence in this group, with mean time to local failure of 9 months and distant failure of 10.5 months; the mean OS for three patients was 12.7 months. Overall, 4 patients had isolated local relapse, 2 developed distant metastases and 2 experienced both local and distant failure. Common sites of distant failure being liver followed by lung and bone.

Although the mean DFS and OS were longer in patients undergoing primary surgery (30.4 and 34.3 months, respectively) compared to those treated with definitive CCRT (25.5 and 26.1 months, respectively), their difference did not reach statistical significance, by using unpaired t-test show p=0.63 for DFS and p=0.34 for OS. However, the numerical trend favours the surgery group in both DFS and OS. Additionally, failure pattern differed slightly between two groups, with a numerically higher failure rate observed in the surgical group (5 patients, 41.6% vs 3 patients, 13.6%), possibly reflecting histological aggressiveness.

Table 1. Patient Characteristics and Treatment details (n=34)

Characteristic	**Number of patients (n)**	**Percentage (%)**
Age at presentation (years)		
Mean / Range	48.6 / 33 - 70	
31 - 40	8	23.5
41 - 50	14	41.2
51 - 60	8	23.5
61 - 70	4	11.8
Histology		

Adenocarcinoma (AC)	21	61.8
Adenosquamous carcinoma	7	20.6
AC with Neuroendocrine differentiation	1	2.9
AC with papillary serous type	1	2.9
Leiomyosarcoma	1	2.9
Neuroendocrine Carcinoma	1	2.9
Papillary Squamotransitional carcinoma	1	2.9
Squamotransitional carcinoma	1	2.9
FIGO Stage (2018)		
I	5	14.7
IIA	4	11.8
IIB	13	38.2
IIIB	1	2.9
IIIC1	8	23.5
IVA	3	8.9
Primary treatment		
Definitive CCRT	22	64.7
Primary surgery + Adjuvant RT/CCRT	12	35.3

Table 2: Survival Outcomes

Group	Mean DFS (months)	Mean OS (months)
Entire cohort	27.2	29
Surgery	30.4	34.3
CCRT	25.5	26.1

Discussion

Non-squamous histologies in carcinoma cervix, including adenocarcinoma, adenosquamous carcinoma, and rare subtypes such as neuroendocrine or sarcomatoid variants, represent a biologically and clinically distinct subgroup compared to the predominant squamous cell carcinoma. In our study of 34 patients treated between January 2021 and December 2024, adenocarcinoma was the most common subtype (61.7%), followed by adenosquamous carcinoma (20.5%) and other rare variants.

The median age at presentation was 48.6 years, with the majority in the 41–50 age group. This aligns with previously reported trends indicating that adenocarcinoma tends to present in slightly younger patients compared to squamous histology [8]. Most patients presented at advanced stages, with IIB being the most common, followed by IIIC1.

The optimal management for non-squamous histologies remains controversial due to their relatively lower radiosensitivity and higher tendency for distant failure. In our cohort, 12 patients underwent primary surgery, while 22 received radical concurrent chemoradiotherapy. Patients treated with surgery showed a numerically higher mean OS (34.3 months) and DFS (30.4 months) compared to those who received radical CCRT (OS 26.1 months; DFS 25.5 months). Despite this trend, the difference did not reach statistical significance, likely due to the small sample size.

Failure patterns also varied between the two groups. Among surgical patients, 5 experienced relapse (local or distant), with a shorter time to distant failure (mean: 5.7 months). In the CCRT subgroup, 3 patients relapsed, with a slightly delayed mean time to distant failure (10.5 months), although these differences were not statistically significant. The OS for those who experienced relapse was notably poor in both groups (14.6 months post-relapse in the surgery group vs. 12.7 months in CCRT group).

Our findings are in concordance with global data suggesting that adenocarcinoma and adenosquamous histologies have inferior local control and survival outcomes compared to squamous carcinoma. Studies such as by Yokoi et al. and Seamon et al. have highlighted the limitations of radiotherapy in these subtypes, with surgical intervention offering better control in early-stage disease. However, for locally advanced disease, concurrent chemoradiation remains the standard of care, though with modest outcomes[9,10] [11,12].

The increasing recognition of HPV-independent pathways, particularly in non-squamous histologies like gastric-type adenocarcinoma and clear cell carcinoma, further underscores the need for molecular profiling and personalized treatment strategies[13]. Although HPV is implicated in the pathogenesis of most adenocarcinomas, certain subtypes are HPV-negative and carry a worse prognosis[14,15].

Limitations

This study is limited by its retrospective nature and small sample size. Additionally, the histological heterogeneity within the non-squamous category makes outcome comparisons complex. Prospective multicentric studies with molecular correlation are warranted to validate the findings.

Conclusion

Non-squamous histologies in carcinoma cervix represent a high-risk subgroup with relatively poorer outcomes. While primary surgery may offer survival benefits in selected cases, especially in early-stage disease, the role of chemoradiation remains central in locally advanced cases. Tailored strategies, including adjuvant therapy and molecular-based risk stratification, may help improve outcomes in the future.

Declaration of patient consent

Consent forms obtained from all patients appropriately in which they have given their consent for clinical information to be reported in the study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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