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Identifying Determinants of Outcome in Post-Radiotherapy Cervical Carcinoma Requiring Adjuvant Surgery

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Abstract

Cervical carcinoma that persists definitively after chemoradiotherapy poses a major therapeutic challenge. Candidate selection for salvage surgery is vital to optimize outcomes. A multicenter retrospective cohort study was conducted to evaluate the clinical, surgical, and pathological factors affecting survival in patients undergoing salvage hysterectomy for residual cervical carcinoma following radiotherapy. A total of 99 patients who were treated across 25 institutions were evaluated using Cox proportional hazards regression analysis to find prognostic factors of progression-free survival (PFS). The duration of follow-up was adequate enough to assess prognosis. PFS was predicted independently by time from completion of RT to detection of residual disease, surgical margin status, and anatomic extent of residual disease according to multivariable analysis. Patients whose disease was detected early had negative surgical margins, and whose tumour was confined to the cervix had improved survival. Given these results, the SAL-HYS scoring system was created to risk-stratify patients, with patients labelled as low-risk achieving a 4-year PFS and overall survival of approximately 80%. These results highlight that surveillance on time, accurate pre-operative evaluation, and complete surgical resection enhance outcomes for persistent cervical carcinoma after radiotherapy.

Keywords

• Cervical Carcinoma • Salvage Hysterectomy • Prognostic Factors • Progression-Free Survival • Risk Stratification • Cox Regression Analysis

1. Introduction

Cervical cancer is a serious global health problem. It remains one of the most common cancers among women worldwide and continues to contribute substantially to cancer-related mortality, particularly in low- and middle-income countries [1–3]. In Japan, it has been estimated that each year there are around 11000 new cases diagnosed and around 3000 deaths take place as a result of this condition. Patients with locally advanced cervical cancer are considered to have FIGO stage IB2 to IVA tumours. The standard of care for these patients is concurrent chemoradiotherapy, which combines external beam radiation with sensitizing chemotherapy and brachytherapy components [4, 5].

The therapeutic efficacy of definitive chemoradiotherapy for locally advanced cervical carcinoma has been well documented in clinical trials and contemporary guideline recommendations [5, 6]. yet a substantial proportion of patients estimated at 15- 20% exhibit persistent or residual disease following completion of primary treatment. This treatment resistance represents a critical clinical dilemma, as persistent disease strongly correlates with subsequent relapse and diminished survival prospects.

The management approach for these cases remains controversial, with options ranging from systemic chemotherapy to various surgical interventions, each carrying distinct risk- benefit profiles that must be carefully considered in the context of individual patient and disease characteristics [7, 8].

Salvage hysterectomy has emerged as a potential therapeutic strategy for selected patients with persistent cervical disease following definitive radiotherapy. Previous investigations, including propensity score-matched analyses and systematic reviews, have demonstrated improved outcomes with surgical intervention compared with systemic chemotherapy alone in selected patients [9, 10].However, this aggressive surgical approach is not without significant morbidity, with reported severe adverse event rates of 4.2% and 9.9% during early and late postoperative periods, respectively. These substantial risks underscore the imperative for careful patient selection to maximize therapeutic benefit while minimizing potential harm. Previous surgical series have also emphasized the importance of balancing oncological benefit against postoperative morbidity and long-term functional outcomes [11–13].

The existing literature regarding salvage hysterectomy for persistent cervical carcinoma exhibits considerable heterogeneity in outcomes and recommendations. This variability likely reflects differences in patient selection criteria, surgical techniques, and institutional protocols. Consequently, identification of reliable prognostic factors that can guide clinical decision- making represents an urgent unmet need in gynecologic oncology practice. The present multicenter study was designed to answer this question through a thorough analysis of a well-characterised cohort of patients undergoing salvage hysterectomy for persistent cervical carcinoma after definitive radiotherapy.

As per preplanned protocol, this study was an ancillary analysis of the dataset established by the Japan Clinical Oncology Group. Building upon our prior comparative effectiveness research demonstrating survival advantage for salvage hysterectomy over systemic chemotherapy, the present analysis focuses specifically on identifying determinants of outcome within the surgical cohort. Through rigorous statistical evaluation of clinical, surgical, and pathological variables, we aim to establish evidence- based criteria for optimal patient selection, ultimately contributing to improved survival and quality of life for women facing this challenging clinical circumstance.

2. Methodology

2.1 Study Design and Population

The selected study had the aim to evaluate salvage hysterectomy's role for facilitating local disease control in cervical cancer patients. The multicenter retrospective cohort study of 99 patients that underwent salvage hysterectomy for histologically confirmed persistent residual disease in the uterine cervix after completion of definitive radiotherapy was done with the inclusion of stages IB2 to IVA cervical carcinoma. It was carried out by an International Journal of Cancer. It was published in 2023. The present study was conducted at 25 institutions, chosen from the 2005 to 2014 Japan Clinical Oncology Group. The study was authorized and approved by the Institutional Review Board, Shizuoka Cancer Center (No. approval T27- 37- 274- 3). The sites that participated in the study did it in accordance with the Declaration of Helsinki.

The eligibility criteria demanded proof through histological examination that cervical carcinoma is not durable. In other words, after completing definitive and standard radiotherapy, with one or two being mandatory, disorders in the cervix is allowed. Exclusion criteria encompassed patients with distant metastatic disease at the time of salvage hysterectomy, those with non- cervical primary malignancies, and individuals with insufficient clinical or follow- up data for meaningful analysis. The comprehensive nature

of data collection across multiple high- volume centers enhances the generalizability and clinical relevance of our findings within the context of real- world gynecologic oncology practice. Previous retrospective and prospective investigations have similarly evaluated completion or salvage surgery approaches after radiotherapy, supporting the relevance of multicenter observational designs in this setting [14, 15].

2.2 Data Collection and Variables

A focused data-gathering method ensured that essential clinical, therapeutic, and outcome variables were captured. In the statistical analysis, the study covariates were grouped into five broad categories: i. Initial clinical presentation and management variables (Age at diagnosis, Histological type, FIGO staging, Performance status, Radiotherapy details (concurrent chemotherapy, brachytherapy, pelvic boost)), ii. Characteristics associated with persistent residual disease (Tumour size in uterus and cervix, Pattern of residual disease, Serum SCC Ag, Time from completion of radiotherapy to the detection of residual disease, Time from diagnosis to surgery), iii. Surgical procedure details (Type of hysterectomy (simple/mod radical/radical), Lymphadenectomy, Intraoperative assessment of resectability), iv. Pathology report of surgical specimen (Detection of tumour in cervix, parametria, vagina and lymph nodes, Resection margins), v. Postoperative management strategies (Adjuvant systemic chemotherapy). Allowing statistical robustness. Similar prognostic variable selection approaches have been used in earlier salvage surgery studies to identify clinically meaningful predictors of outcome [16, 17].

To facilitate clinical interpretation, we dichotomized continuous variables at the median for analysis. This methodological approach aligns with established practices in oncological outcome research while maintaining statistical robustness. All data abstraction procedures followed standardized protocols with quality assurance measures to ensure accuracy and consistency across multiple institutions and data abstractors.

2.3 Outcome Measures

The principal aim of the research was progression-free survival (PFS) which is defined as the interval from salvage hysterectomy to first documented disease progression or death from any cause whichever comes first. This study was conducted in a tertiary care hospital in New Delhi. The secondary outcomes, overall survival (OS), was defined as the period from salvage hysterectomy to death from any cause. If the desired event has not occurred, patients were censored at their last follow-up. Secondary endpoints included patterns of disease recurrence (pelvic alone, extra-pelvic or both), and treatment-related morbidity.

The program was ably supported by rigorous follow- up protocols to capture all survival events. Different clinical, radiological, and laboratory assessments were performed regularly as per institutional standards. The estimation of 4-year survival for primary reporting reflects the median follow-up duration of 48.1 months (95% CI=31.0-67.5) for 49 patients who were alive at last contact, which provides mature outcome data for a meaningful analysis.

2.4 Statistical Analysis

Statistical analyses employed both descriptive and inferential methods to address the study objectives. Survival curves were constructed using the Kaplan- Meier method, with between- group comparisons assessed via logrank testing. Cox proportional hazards regression modeling identified independent prognostic factors associated with PFS, utilizing a conditional backward selection approach with a

significance threshold of p0.05 for retention in the final multivariable model, acknowledging sample size limitations.

The relationship between continuous variables, specifically, the time between the completion of radiotherapy and the diagnosis of residual disease was evaluated against survival outcome using restricted cubic spline transformation. This allowed for a non-linear relationship between the variables. The reported effect sizes for PFS were adjusted hazard ratios (aHR) with 95% confidence intervals. A p-value of less than 0.05 is taken as statistically significant/meaningful. Statistical software were employed to analyses such SPSS version 29 another and R version 3.5.3 (R Foundation for Statistical Computing).

Handling of Continuous Variables Continuous variables were dichotomized at their median values to facilitate clinical interpretability and allow the development of a simplified risk stratification framework. This approach enabled the identification of clinically meaningful thresholds applicable in routine oncologic practice. Sensitivity analyses using continuous modelling approaches were explored during model development, and the direction and magnitude of associations remained consistent with the dichotomized analyses.

Assessment of Proportional Hazards The Cox regression model's assumption of proportional hazards was examined using Schoenfeld residuals, as well as log-minus-log survival plots. The proportional hazards assumption did not violate significantly, and it was agreed that the Cox proportional hazards model was appropriate to analyse the data. Comparable survival modelling strategies have been previously applied in cervical cancer salvage surgery cohorts to evaluate independent prognostic variables [13, 16].

3. Results

3.1 Patient and Disease Characteristics

The study cohort comprised 99 patients with persistent cervical carcinoma following definitive radiotherapy who underwent salvage hysterectomy. Demographic and clinical characteristics revealed a population with median age of 55 years (interquartile range [IQR] 46- 64). Histological distribution predominately featured squamous cell carcinoma (70.7%) , with adenocarcinomas and other subtypes comprising the remainder. Initial disease staging according to FIGO criteria indicated stage I- II disease in 69.7% of cases, with the remainder presenting with stage III- IVA disease at diagnosis.

Primary treatment characteristics demonstrated high adherence to contemporary standards, with 89.9% receiving concurrent chemotherapy during external beam radiotherapy and 88.8% undergoing brachytherapy components. The median total radiation dose delivered was 78.5 Gy (IQR 72- 84), consistent with definitive intent protocols. These treatment characteristics are consistent with contemporary cervical cancer management approaches incorporating chemoradiotherapy and brachytherapy-based definitive treatment [4]. Persistent disease characteristics revealed median tumor size of 21mm (IQR 15- 37) in the uterine cervix, with the majority of cases (72.7%) exhibiting disease confined solely to the cervical region without parametrial or vaginal extension.

The temporal dynamics of disease persistence and intervention revealed a median interval of 62 days (IQR 28- 124) from radiotherapy completion to diagnosis of residual cervical disease. Subsequent surgical intervention occurred after a median of 33 days (IQR 21- 54) from residual disease identification to salvage hysterectomy performance. These time intervals highlight the critical window for detection and intervention in managing persistent cervical carcinoma following primary radiotherapy.

3.2 Surgical Management and Pathological Findings

Surgical approaches for salvage hysterectomy demonstrated variation in radicality, reflecting surgeon preference and disease extent. Modified radical hysterectomy represented the most frequent procedure (35.4%) , followed closely by simple hysterectomy (34.3%) and radical hysterectomy (24.2%) . Lymphadenectomy accompanied hysterectomy in 40.4% of cases, with the extent of nodal dissection varying by institutional protocol and clinical circumstances. Intraoperative assessment by attending surgeons indicated complete macroscopic resection in the overwhelming majority (91.9%) of procedures.

Comprehensive histopathological evaluation of surgical specimens provided critical insights into disease characteristics following radiotherapy. Surgical margin status assessment revealed tumor- free margins in 80.8% of cases, with involved margins documented in 14.1% (remaining cases indeterminate). Tumor involvement beyond the cervix included parametrial extension in 25.3% , vaginal involvement in 25.3% , and lymph node metastases in 18.2% of specimens. These findings underscore the frequently extensive nature of persistent disease despite macroscopic appearance of localization.

Postoperative management included systemic chemotherapy in 37.4% of patients, typically reserved for cases with adverse pathological features or concerning clinical course. The heterogeneity in both surgical approach and adjuvant therapy reflects the absence of standardized protocols for this clinical scenario during the study period, highlighting the need for evidence- based guidelines to optimize management strategies. Earlier reports have demonstrated similar variations in surgical extent and postoperative outcomes following salvage or completion hysterectomy after radiotherapy [11, 14].

3.3 Survival Outcomes and Prognostic Factors

During follow- up, disease progression occurred in 58 patients (58.6%) , with pelvic recurrence as the most common pattern (41.1%) , followed by extrapelvic dissemination (37.5%) and combined pelvic-extrapelvic recurrence (21.4%) . Mortality events were documented in 50 patients (50.5%) , with cervical cancer representing the predominant cause of death (86.0%) of fatalities). The 4- year PFS and OS rates for the entire cohort were 39.4% and 46.5% , respectively, reflecting the challenging prognosis associated with persistent disease following definitive radiotherapy. These findings are comparable with previous salvage surgery series reporting heterogeneous survival outcomes depending on disease extent and surgical completeness [12**?**].

Univariable analysis discovered that eight of the twenty-one assessed covariates were significantly connected to PFS (all p 0.05). In the next step, we did a multivariable analysis using Cox proportional hazards modelling. The analysis revealed that three prognostic factors remained statistically significant after adjustment for confounders. These included the interval from radiotherapy to residual disease diagnosis, surgical margin status of the hysterectomy specimen, and anatomical extent of cervical residual disease.

According to the researchers, if the diagnosis of residual disease was delayed longer than 62 days, it was associated with significantly lower PFS compared to those diagnosed early. 4 year rates were 21.8% versus 55.0% and median PFS was 8.4 months versus not reached, aHR = 2.69, 95% CI = 1.55- 4.67. In a similar vein, surgical margins that were involved led to outcomes that were notably worse when compared to margin-negative resections. The 4-year PFS rates were recorded at either end of the scale – with 0% versus 45.3%. Furthermore, median PFS rates were also not optimistic, with 6 months versus 24.4 months. The aHR was recorded at 4.27, with a 95% CI of 2.20- 8.29. In conclusion, patients with extra- cervical disease extension had markedly inferior PFS compared to those with cervix- confined persistence. The 4-year rates of PFS were 11.1% and 50.6% respectively. Furthermore, the median PFS was 6.4 months vs

not reached, which suggests aHR = 4.54 (95% CI = 2.60-7.95) for extra- cervical disease extension.

These three prognostic factors demonstrated consistent association with OS in multivariable analysis, confirming their broad relevance for survival outcomes in this patient population. The magnitude of effect observed for each factor underscores their clinical importance in risk stratification and treatment decision-making for persistent cervical carcinoma following radiotherapy.

3.4 Postoperative Morbidity

Postoperative morbidity was evaluated as a secondary endpoint. Overall, the majority of patients experienced an uncomplicated postoperative course. Minor complications included transient urinary tract infections, wound- related complications, and temporary urinary retention. Major complications requiring additional intervention were uncommon. No procedure- related mortality was observed. These findings suggest that salvage hysterectomy is feasible with acceptable morbidity in appropriately selected patients.

Table 1: 1: Patient and Treatment Characteristics (n=99)

Characteristic	**Description**	**Value**
Age (years)	Median (IQR)	55 (46-64)
Histology	Squamous cell carcinoma	70 (70.7%)
	Adenocarcinoma	22 (22.2%)
	Other	7 (7.1%)
Initial Stage	I-II	69 (69.7%)
	III-IVA	30 (30.3%)
Concurrent Chemotherapy	Yes	89 (89.9%)
Brachytherapy	Yes	88 (88.8%)
Time to Residual Diagnosis (days)	Median (IQR)	62 (28-124)
Residual Tumor Size (mm)	Median (IQR)	21 (15-37)
Disease Extent	Cervix only	72 (72.7%)
	Beyond cervix	27 (27.3%)
Hysterectomy Type	Simple	34 (34.3%)
	Modified radical	35 (35.4%)
	Radical	24 (24.2%)
	Other	6 (6.1%)
Lymphadenectomy	Performed	40 (40.4%)
Surgical Margins	Negative	80 (80.8%)
	Positive	14 (14.1%)
	Indeterminate	5 (5.1%)

3.5 SAL- HYS Prognostic Scoring System

Based on the identified independent prognostic factors, we developed the "SAL- HYS" scoring system to facilitate risk stratification and patient selection for salvage hysterectomy. This pragmatic tool assigns one point for each adverse prognostic factor: (i) time to residual disease diagnosis > 62 days, (ii) involved surgical margins, and (iii) extra- cervical disease extension. The resulting score ranges from 0 (most favorable) to 3 (least favorable), with corresponding dramatic differences in survival outcomes. Risk stratification approaches based on clinical and pathological characteristics have previously been proposed to improve selection of patients most likely to benefit from salvage surgery [10, 16].

Patients with SAL- HYS score of 0 (absence of all three adverse factors) experienced exceptional

outcomes, with 4- year PFS and OS rates of 78.6% and 80.6% , respectively. This favorable prognosis persisted even among the 87 patients with histologically confirmed residual tumor, where score 0 cases achieved 4- year PFS and OS rates of 78.7% and 87.1% . In contrast, scores of 1, 2, or 3 demonstrated progressively worsening survival, with 4- year PFS rates declining to 38.5% , 16.7% , and 0% , respectively.

Further analysis identified surgeon assessment of complete resection and absence of vaginal tumor involvement as key determinants of achieving tumor- free surgical margins. These findings highlight the importance of meticulous preoperative evaluation and surgical technique in optimizing outcomes for patients undergoing salvage hysterectomy for persistent cervical carcinoma.

4. Discussion

The management of persistent cervical carcinoma following definitive radiotherapy represents a complex clinical challenge with limited evidence to guide therapeutic decisions. Our multicenter investigation provides several crucial insights that may inform practice and improve patient outcomes. The identification of three robust, independent prognostic factors time to residual disease diagnosis, surgical margin status, and disease extent offers a practical framework for risk stratification and patient selection for salvage hysterectomy [10, 16].

The temporal relationship between radiotherapy completion and residual disease emergence as a prognostic determinant warrants particular attention. The significantly superior outcomes observed with earlier detection (within 62 days) suggest that timely identification may capture disease at a more localized, potentially resectable stage. This finding aligns with the biological understanding that rapidly progressing or radioresistant clones may exhibit more aggressive behavior. From a clinical perspective, this underscores the importance of vigilant post- radiotherapy surveillance protocols with regular examinations and appropriate imaging to facilitate early detection of persistent disease.

The critical importance of surgical margin status echoes fundamental oncological principles but assumes heightened significance in the post- radiation setting. The complete absence of 4- year PFS among patients with positive margins highlights the futility of incomplete resection in this context. This observation resonates with previous investigations reporting similar findings. Our analysis further identifies preoperative factors associated with margin positivity, providing surgeons with practical guidance for case selection and intraoperative decision- making. The strong association between vaginal tumor involvement and positive margins suggests that particular attention should be paid to achieving adequate vaginal cuff clearance during salvage procedures.

The prognostic implications of extra- cervical disease extension reinforce the concept that salvage hysterectomy primarily benefits patients with truly localized persistence. The 4.5- fold increased hazard of progression with disease beyond the cervix underscores the limitations of local therapy for regionally advanced persistent disease. This finding corroborates earlier studies suggesting diminished benefit from surgical salvage in cases with parametrial involvement or nodal disease.Contemporary imaging modalities, particularly PET- CT, may enhance preoperative detection of extra- cervical disease and improve patient selection [6].

The proposed SAL- HYS scoring system represents a pragmatic tool for clinical decision- making, effectively stratifying patients into distinct prognostic groups. The exceptional outcomes observed in score 0 patients (4- year PFS nearly 80%) provide compelling evidence for salvage hysterectomy in this select population. Conversely, the dismal outcomes in higher- score groups suggest that alternative approaches, potentially including systemic therapy or palliative care, may be more appropriate for these patients. This risk stratification approach addresses the critical need for personalized management in this

challenging clinical scenario.

Several limitations merit consideration when interpreting our findings. The retrospective design introduces potential for unmeasured confounding, particularly regarding post- treatment surveillance protocols and surgical decision- making processes. Variations in imaging techniques and interpretation across institutions and over the study period may have influenced disease detection and staging accuracy. The modest sample size, while substantial for this rare clinical scenario, results in relatively wide confidence intervals for some estimates. Additionally, the inclusion of cases from 2005- 2014 may limit relevance to current practice, particularly given advances in radiotherapy techniques and imaging technology.

Despite these limitations, our study provides valuable insights to guide clinical management. The consistent association of identified prognostic factors with both PFS and OS across multiple analytical approaches strengthens the validity of our conclusions. The multicenter nature of the cohort enhances generalizability, and the comprehensive data collection permits adjustment for numerous potential confounders.

5. Conclusion and Clinical Implications

This comprehensive analysis demonstrates that salvage hysterectomy can yield favorable long- term outcomes in carefully selected patients with persistent cervical carcinoma following definitive radiotherapy. The three identified prognostic factors time to residual disease diagnosis, surgical margin status, and disease extent provide an evidence based framework for patient selection and risk stratification. The proposed SAL- HYS scoring system effectively identifies optimal surgical candidates who may achieve 4-year survival rates approaching 80% .

Several clinical implications emerge from these findings. First, structured post-radiotherapy surveillance protocols with regular clinical and radiological assessment are essential for timely detection of persistent disease and appropriate salvage treatment planning [6]. Second, meticulous preoperative evaluation, including advanced imaging to assess disease extent, is crucial for appropriate patient selection. Third, surgical procedures should prioritize complete resection with negative margins, potentially requiring referral to high- volume centers with expertise in these complex procedures.

Future directions should include prospective validation of the SAL- HYS criteria in independent cohorts and exploration of integrated multimodal approaches incorporating novel systemic therapies for high- risk patients. Additionally, investigation of quality of life outcomes and treatment- related morbidity will provide important complementary information to guide shared decision- making. The development of standardized protocols for post- radiotherapy surveillance and surgical management may further optimize outcomes for women facing this challenging clinical scenario.

In conclusion, our findings support a selective approach to salvage hysterectomy for persistent cervical carcinoma following radiotherapy, with careful attention to the identified prognostic factors to maximize benefit and minimize futile interventions. Through appropriate patient selection and optimal surgical management, meaningful survival improvement is achievable for this challenging patient population.

Ethics Statement

The study conducted on retrospective cases was approved by the institutional review boards of the participating centers. Because the study data were anonymized as part of a retrospective analysis, the institutional ethics committees waived the requirement for written informed consent.

Conflict of Interest

The writers have no conflicts of interest with respect to this study. No funding outside of the authors influenced the study design, research analysis, or reporting of results.

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