Title

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Journal

Gynecologic Oncology, 162(3)

ISSN

0090-8258

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Publication Date

2021-09-01

DOI

10.1016/j.ygyno.2021.06.017

HHS Public Access

Author manuscript

Gynecol Oncol. Author manuscript; available in PMC 2022 September 01.

Published in final edited form as:

Gynecol Oncol. 2021 September ; 162(3): 532–538. doi:10.1016/j.ygyno.2021.06.017.

Beyond Sedlis—A novel histology-specific nomogram for predicting cervical cancer recurrence risk: An NRG/GOG ancillary analysis

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Study concept for design: AFR, ANF, KL, AB, AV
Provision of materials or patients: DM, OR, NS
Acquisition of data: DM, KL, OR, NS, AB
Analysis and interpretation of data: AFR, LVL, ANF, KL, AB, SW
Manuscript writing: ANF, KL, AB
Critical review of manuscript: AFR, AW, LM, DM, LVL, ANF, YC, KL, OR, WKH, NS, AB, MK, AV, SW, YL
Final approval of manuscript: AFR, AW, LM, DM, LVL, ANF, YC, KL, OR, WKH, NS, AB, MK, AV, SW, YL

CONFLICTS OF INTEREST

Dr. Van Le reports royalties from Wolters Kluwer (as an editor of TeLinde's textbook). Dr. Huh reports money paid to him from consultancy with DYSIS. Dr. Miller reports money paid to him from consultancy with Tesaro, Eisai, Incyte, Karyopharm, and Genentech as well as money paid to his institution from Merck. He also reports money paid to his institution from grants or grants pending with nVision Medical, Advenchen, Forty Seven, Merck, Syros, and US BIOTEST. Dr. Ragab reports money paid to him from Consultancy with Regeneron. Dr. Viswanathan reports employment with money paid to her from Elsevier as the Ediotr in Chief for Seminars in Radiation Oncology. She also has an R01 NIH grant with money to her institution, and she received textbook royalties from Springer. Dr. Tewari has received money paid to him from consultancy with Clovis, Merck, Abbvie, Amgen, GSK, and Astra-Zenega, as well as payment for lectures from Clovis, Merck, Abbvie, Amgen, GSK, Astra-Zenega
Drs. Levinson, Fader, Beavis, Wolfson, Waggoner, Guntupalli, Lee, Kelly, McNally, Casablanca, Rositch, Spirtos, Wilkinson, Holman and Chris Purdy have no financial disclosures.

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Abstract

Purpose: The Sedlis criteria define risk factors for recurrence warranting post-hysterectomy radiation for early-stage cervical cancer; however, these factors were defined for squamous cell carcinoma (SCC) at an estimated recurrence risk of ≥30%. Our study evaluates and compares risk factors for recurrence for cervical SCC compared with adenocarcinoma (AC) and develops histology-specific nomograms to estimate risk of recurrence and guide adjuvant treatment.

Methods: We performed an ancillary analysis of GOG 49, 92, and 141, and included stage I patients who were surgically managed and received no neoadjuvant/adjuvant therapy. Multivariable Cox proportional hazards models were used to evaluate independent risk factors for recurrence by histology and to generate prognostic histology-specific nomograms for 3-year recurrence risk.

Results: We identified 715 patients with SCC and 105 with AC; 20% with SCC and 17% with AC recurred. For SCC, lymphvascular space invasion (LVSI: HR 1.58, CI 1.12–2.22), tumor size (TS ≥4cm: HR 2.67, CI 1.67–4.29), and depth of invasion (DOI; middle 1/3, HR 4.31, CI 1.81–10.26; deep 1/3, HR 7.05, CI 2.99–16.64) were associated with recurrence. For AC, only TS ≥4cm, was associated with recurrence (HR 4.69, CI 1.25–17.63). For both histologies, there was an interaction effect between TS and LVSI. For those with SCC, DOI was most associated with recurrence (16% risk); for AC, TS conferred a 15% risk with negative LVSI versus a 25% risk with positive LVSI.

Conclusions: Current treatment standards are based on the Sedlis criteria, specifically derived from data on SCC. However, risk factors for recurrence differ for squamous cell and adenocarcinoma of the cervix. Histology-specific nomograms accurately and linearly represent risk of recurrence for both SCC and AC tumors and may provide a more contemporary and tailored tool for clinicians to base adjuvant treatment recommendations to their patients with cervical cancer.

Keywords

cervical cancer; adenocarcinoma; stage I; adjuvant radiation

INTRODUCTION

Cervical cancer is the fourth most frequently diagnosed malignancy and is among the leading causes of cancer-related death in women [1,2]. While radical hysterectomy is the mainstay of treatment for women with early-stage disease, select women benefit from adjuvant radiation to further reduce their risk of cancer recurrence. Identifying those patients who will benefit from post-operative radiation is critical to reduce morbidity and mortality from this disease [3].

One of the first cooperative group studies to identify these patients was GOG 49, which identified tumoral depth of invasion (DOI), parametrial involvement, lymphvascular space invasion (LVSI), tumor grade, and gross vs. occult tumor, as factors associated with lymph node involvement in clinical stage I cervical cancers [4]. A subsequent analysis of squamous cell carcinoma (SCC) only, suggested that DOI, LVSI, and tumor size (TS) most significantly impact recurrence risk [5]. This analysis of SCC patients formed the basis of GOG 92, which randomized women considered “intermediate risk” - defined as combinations of DOI, LVSI, and TS that predicted a 3-year recurrence of ≥30% - to adjuvant radiation or observation. Published by Sedlis et al in 1999, the trial demonstrated a significant reduction in recurrence from 28% to 15% with adjuvant radiation therapy in women with “intermediate risk” factors (Appendix 1) [3]. While this model successfully predicted a reduction in recurrence in a population of almost entirely SCC, it is designed to trigger adjuvant treatment only for those patients with a recurrence risk of >30%. Furthermore, like GOG 49, GOG 92 primarily included patients with SCC.

The majority of cervical cancer research has focused on SCC of the cervix, often grouping other, rarer histologic subtypes together with SCC. Recent population-based studies suggest that incidence rates of adenocarcinoma (AC) of the cervix have increased almost 30% from 1973 to 1996, now comprising approximately 25% of all cervical cancers diagnosed annually in the United States [6]. Cervical AC differs from SCC in many ways including the associated risk factors, response to therapy, and overall prognosis [7–10]. Importantly, the differences in response to radiation also appear to be different for cervical AC [11]. In a follow-up analysis of GOG 92 with 10 years of follow-up, recurrence was higher in women who were observed with AC (44%) vs those observed with SCC (28%), suggesting that the Sedlis criteria accurately predicted a 30% recurrence rate of SCC, but may not be as applicable to AC. Additionally, the benefit from radiation was greater in those women with AC compared to SCC, with a risk reduction from 44% to 9% for AC and only 28% to 20% for SCC [12].

Other ancillary studies have attempted to delineate the impact of histologic subtype on recurrence risk by including histology as a covariate, rather than stratifying analyses by histologic subtype [13]. As such, any differential response to treatment by histology has not been evaluated. A re-analysis, helping to inform an improved model for adjuvant

treatment of early cervical cancer is needed, that recognizes AC distinct from SCC. We, therefore, aimed to determine and compare risk factors for recurrence specific to SCC and AC and to develop a histology-specific nomogram for each histologic subtype to best predict recurrence risk in order to better inform the appropriate population that might benefit from adjuvant treatment.

METHODS

Based on the available cooperative group data, we performed a post hoc exploratory study of patients enrolled in National Cancer Institute GOG trials 49 (a prospective analysis of stage I patients evaluating lymph node involvement) [4], GOG-92 (a randomized trial evaluating adjuvant radiation for stage I patients) [3], and GOG-141 (a randomized trial in which women with bulky stage IB cervical cancer received surgery alone vs. neoadjuvant chemotherapy plus surgery) [14]. These three studies were included in the current analysis as they all evaluated patients with stage I disease who were treated with surgery alone, regardless of risk factors for recurrence. We included Stage I patients with SCC and AC, who did not undergo neoadjuvant or adjuvant treatment, and who had negative lymph node assessments and negative surgical margins. Patients with subtypes defined as adenocarcinoma unspecified, endometrioid adenocarcinoma, mucinous adenocarcinoma, villoglandular adenocarcinoma, and serous adenocarcinoma were classified as AC; patients with squamous cell carcinoma were classified as SCC. Patients with adenosquamous carcinoma were excluded in this analysis, as these patients have been shown to be both epidemiologically and prognostically different than AC [7].

Patient demographics, tumor characteristics, and clinical outcomes were abstracted from the records of each study. Demographic characteristics included age, race (White, Black, Asian), and GOG performance status. Tumor characteristics based on surgical specimens included tumor grade (1, 2, or 3), LVSI (present/absent), depth of tumoral invasion (inner 1/3, middle 1/3, or deep 1/3), and TS (<2cm, 2–4cm, or ≥4cm). Any missing demographic or tumor data was separately categorized. Demographic and tumor characteristics were compared between histologic subtypes using T-tests and chi-square tests for continuous and categorical variables, respectively.

The primary outcome evaluated was time to disease recurrence, or recurrence-free survival (RFS). Three-year recurrence rates were calculated from the date of trial enrollment to the date of first recurrence. Cox proportional hazards regression models were created including known clinical risk factors for recurrence: LVSI (present/absent), TS (<2cm, ≥2cm and <4cm, ≥4cm), and DOI (inner, middle, outer third). The models were stratified by histologic subtype to examine the differential effect of each of these factors in SCC and AC. The proportional hazards assumption was checked using the Kolmogorov type supremum test. The model evaluation process blended a combination of factors with known clinical relevance, statistical significance in at least one of the histologic subtypes and model evaluation metrics (i.e. area under the curve). Three-year RFS for each distinct combination of risk factors was predicted for both histologic subtypes. RFS curves were generated for select combinations of predictor variables to illustrate differences between the models based on histologic subtypes.

A prognostic histology-specific nomogram for 3-year recurrence was developed using the results of the Cox proportional hazards models for each histologic subtype. The 3-year recurrence probabilities were regressed in a general linear model. The parameters generated by this model were used to inform the variables in the histology-specific nomograms. A series of linear models were tested in order to select the nomogram that minimized the error between the predicted values produced by the proportional hazards regression model and was also easily interpretable. For both nomograms, the optimal variable combination included an interaction term between lymphovascular invasion and TS. All analyses were performed using SAS Enterprise Guide 8.1.

RESULTS

In total, there were 820 patients identified with stage I cervical cancer who had negative lymph nodes, negative tumor margins, and who received no neoadjuvant or adjuvant treatment; 715 patients had a diagnosis of SCC and 105 patients had AC. In total, 160 (19%) patients experienced a disease recurrence; 142/715 (20%) patients with SCC and 18/105 (17%) patients with AC. There was no significant difference in mean age, distribution of race, or GOG performance status between the SCC and AC cohorts. Tumor characteristics differed by histologic subtype. SCC tumors had LVSI more often compared to AC tumors, 41% versus 24%, ($p<0.01$). SCC tumors were also larger ($p<0.01$) and more likely to be high grade ($p<0.01$). In contrast, distribution of DOI was similar between SCC and AC, with approximately a third of tumors exhibiting superficial, middle, and deep third invasion (Table 1).

Upon evaluating the impact of various risk factors on RFS by histologic subtype, varying factors were noted to impact recurrence. For SCC, LVSI, DOI, and TS were all significantly associated with recurrence to varying degrees. Depth of invasion had the largest impact on recurrence with hazard ratios (HRs) for middle 1/3 and outer 1/3 invasion of 4.31 [95% confidence interval (CI) 1.81–10.26] and 7.05 (95% CI 2.99–16.64), respectively. On multivariate analysis, for AC, only TS ≥4cm, was independently associated with recurrence (HR 4.69 [95% CI 1.25–17.63]) (Table 2). The Kolmogorov-type Supremum Tests confirmed the proportional hazards assumption was not violated in these models. The time-dependent ROC curves for the Cox proportional hazards model for SCC and AC at 3 years predicted recurrence with 76% and 75% accuracy for SCC and AC, respectively.

Three-year RFS for all predictor variable combinations were evaluated. DOI and TS had a differential impact on RFS depending on histologic subtype (Table 3). TS more greatly impacting RFS for those with AC, while DOI more greatly impacted RFS for those with SCC. For example, for patients with positive LVSI and superficial DOI, a difference in TS of <2cm versus ≥4cm did not greatly impact RFS for those with SCC: HR 0.97 (CI 0.94 – 0.99) versus 0.91 (CI 0.84 – 0.99) respectively; however, for those with AC (negative LVSI and superficial invasion) a difference in TS of <2cm versus ≥4cm greatly impacted RFS, 0.88 (CI 0.71–1.00) versus 0.55 (CI 0.19 – 1.00) (Figure 1). Alternatively, the impact of DOI on RFS for SCC was particularly pronounced. For example, for those with + LVSI and TS 2–4cm, superficial versus deep invasion led to a reduction in RFS of 0.96 (0.92,1) to 0.73

(0.65,0.81) for SCC, but RFS was similar for those with AC despite the change in DOI 0.65 (0.32, 1.00] versus 0.58 (0.36, 0.96] (Figure 2).

In the histology-specific nomograms, there was an interaction effect identified between LVSI and TS for both SCC and AC (Figures 3&4). This was particularly evident in the relationship between LVSI and TS for AC, such that the recurrence risk for a large tumor (≥4cm) with negative LVSI and superficial invasion is 16% (7.8 points)(Figure 3); whereas the recurrence risk for a large tumor (≥4cm) with positive LVSI and superficial invasion is 36% (12.6 points for TS, 5.4 points for LVSI, 0.2 points for superficial DOI) (Figure 3). For SCC, the recurrence risk for a large tumor (≥4cm) with negative LVSI and superficial invasion was 10% (4.9 points on the nomogram) (Figure 4) compared to a recurrence risk of 16% (5.9 points for TS, 1.8 points for LVSI, 0.2 points for superficial DOI) for a large tumor (≥4cm) with positive LVSI and superficial invasion (Figure 4). For SCC, DOI individually had the greatest impact on recurrence, with deep 1/3 invasion alone conferring a 16% recurrence risk (7.8 points) (Figure 4). For AC, TS ≥4cm alone conferred this greatest risk of recurrence with a 15% risk with negative LVSI and a 25% risk with positive LVSI. LVSI alone conferred only a 4% risk of recurrence for patients with SCC as opposed to a 11% recurrence for AC (Figure 3).

When applying the histology-specific nomograms to hypothetical clinical examples, there are clear differences observed in recurrence risk predictions based on cervical cancer histology. For instance, a hypothetical patient with SCC and tumoral LVSI, superficial invasion, and TS ≥5 cm would have a recurrence rate of 18% per the histology-specific nomogram, but a patient with AC and the same intermediate risk factors for recurrence would have a disease relapse risk of 45% (Table 4). Further, upon evaluating various hypothetical combinations of Sedlis, intermediate risk factors for recurrence, there are several scenarios that would not meet Sedlis criteria for post-hysterectomy radiation but that are predicted to incur a 20–40% risk of recurrence by the current histology-specific nomograms (and would, indeed meet the threshold for adjuvant therapy) (Table 4). For example, a patient with SCC, negative LVSI, deep invasion, and a TS of 4 cm would not meet current Sedlis criteria for adjuvant treatment; however, this patient would meet criteria based on our SCC nomogram, given a 25% risk of recurrence [0.2 points for negative LVSI + 7.8 points for deep invasion + 4.5 points for ≥ 4cm tumor = 12.5 points → 25% risk of recurrence] (Figure 4). When changing the histology to AC and applying the same tumoral risk factors for recurrence, the patient would have a 22% risk of disease relapse [0.2 points for negative LVSI + 3.3 points for deep invasion + 7.4 points for ≥ 4cm tumor = 10.9 points → 21.8% risk of recurrence] (Figure 3). Additionally, a hypothetical patient with AC and tumoral LVSI, superficial invasion, and a 2 cm tumor would, again, not meet Sedlis criteria for adjuvant treatment, but would based on the histology-specific nomoagram, with a 32% risk of recurrence [5.4 points for positive LVSI + 1.8 points for superficial invasion + 9 points for 2 cm tumor = 16.2 points → 32.4% risk of recurrence] (Figure 3).

DISCUSSION

The threshold for consideration of adjuvant radiation treatment of early-stage cervical cancer is currently suggested by an algorithm, the Sedlis criteria, that is based on a combination of

tumoral risk factors for recurrence in patients with SCC who are predicted to have a ≥30% 3-year recurrence risk. This threshold is quite high and potentially excludes many women with cervical cancer in the 15–29% recurrence risk range for consideration of adjuvant therapy who could greatly benefit from it. Our post hoc analysis using the collective data from three GOG cervical cancer randomized trials suggests that the magnitude of impact on recurrence risk of a variety of tumoral factors differs dramatically by histologic subtype, and that single, as well as a combination of tumoral factors, differentially impact this risk. While DOI imparts the most significant recurrence risk for SCC, TS is the most important contributing factor for women with cervical AC. Further, the interaction of TS and LVSI had an even more pronounced effect on recurrence risk of those with AC. Unlike the Sedlis criteria which only recommends adjuvant radiation for women with multiple tumoral factors predictive of recurrence and at a specific risk threshold, our more nuanced, histology-specific nomogram provides a more linear assessment of recurrence risk and suggests that women with just one risk factor for recurrence may benefit from adjuvant therapy. Our study further submits that histology-specific nomograms may have greater utility in identifying women with early-stage cervical cancer at highest risk for recurrence and may thus better inform which patients will most likely benefit from adjuvant therapy.

There has been a recent and substantial shift across gynecologic and other cancer treatment paradigms towards tumor-specific therapies (e.g. based on histology, molecular characterization, genotyping, and epigenetic changes) rather than treatment based solely on disease site of origin. There is growing evidence that SCC and AC of the cervix are biologically quite distinct, confer different recurrence risks and prognoses, and thus, warrant histology-specific treatments. For example, the addition of chemotherapy to radiation for patients with locally advanced AC more significantly impacts survival than for those with locally-advanced SCC [9]. Given these known differences between histologic subtypes, it is not surprising then that the risk factors for recurrence also vary by histology. In an updated report of GOG-92, with a median follow-up of 10 years, Rotman et al not only reported differences in recurrence risk based on cervical cancer histology, but also histology-specific differences in response rates to adjuvant radiation. Those with SCC tumors had a 28% risk of recurrence post-hysterectomy with no further treatment, reduced to a 20% recurrence risk after receiving adjuvant radiation, whereas those with AC who had no further treatment post-hysterectomy had a 44% risk of recurrence which was considerably reduced to 9% for those patients who received adjuvant radiation. Furthermore, once those with adenosquamous carcinoma were excluded, none of those with pure AC receiving adjuvant RT recurred [12]. Both the baseline increased risk of recurrence in women with AC and the increased magnitude of benefit of adjuvant radiation compared to SCC suggest that the criteria and risk/benefit ratio for adjuvant radiation in those with AC cervical cancer differs substantially from those with SCC. Therefore, accurately identifying a patient's recurrence risk in this setting is vital, and our current proposed histology-specific nomograms may provide a more nuanced approach to discerning recurrence risk and threshold for adjuvant radiation than the Sedlis criteria.

In prior studies, histologic subtype was not found to have an impact on recurrence free interval, and only adenosquamous subtype was found to impact survival [13]; however, risk factors specific to AC were not evaluated, and interaction between histology and treatment

was not assessed. Therefore, to our knowledge, this is the first analysis that specifically stratifies the recurrence risk by histology, treating AC as its own disease entity. Further studies are needed to better delineate why DOI has a larger impact on recurrence for women with SCC, and why TS has a larger impact for those with AC. We hypothesize that this may be related to differential mechanisms of invasion and the tumor microenvironment for these respective tumor histotypes. With potential variable means of infiltration and growth, these tumors may respond differently to therapeutic strategies. Additional exploration of AC subtypes is also needed to further determine histologic molecular differences to help guide treatment.

While the studies utilized in this analysis are dated and have limitations in their own right, it would have been unethical to follow patients prospectively without adjuvant treatment in a more contemporary analysis, given the current state of the evidence. While it is important to recognize that these patients were managed many years ago with outdated staging models, treatment models, and radiation techniques, current treatment standards--utilizing the Sedlis critera-- are still based on these same data. This re-analysis is a critical first step to help inform the natural history of disease (only able to be studied in this manner) to help guide further more contemporary studies that can externally validate these findings. Other study limitations include the restricted sample size, particularly of cervical AC patients, and the retrospective nature of the study. Additionally, due to the minimal demographic information collected, we were not able to fully evaluate the impact of race or other factors on recurrence risk. In some prior clinical trials, race has been identified as an important prognostic factor for cervical cancer [16]; however other studies suggest that when other associated factors are accounted for, race itself may have minimal impact on prognosis [17]. Thus, further investigation is needed to better understand the impact of race on prognosis and determine variations by histology. Finally, given the limited number of patients with AC, the power of the study to detect differences is reduced. While multiple risk factors were noted to impact recurrence for SCC, only tumor size was identified as a risk factor for AC.

The study strengths are that it is the first analysis to examine risk factors for recurrence specific to each histologic subtype, and that we pooled data from large prospective studies in order to evaluate the appropriate populations. We excluded those patients with high-risk disease and only evaluated patients who received no adjuvant or neoadjuvant treatment in order to more fully understand the natural history and progression of each of these histologic subtypes. Furthermore, expert pathologists reviewed all specimens and data was collected in the controlled setting of randomized clinical trials.

The results of our analysis suggest that even single tumoral risk factors confer sufficient elevated risk of recurrence for both SCC and AC of the cervix to warrant adjuvant treatment, and these factors differ by histologic subtype. By contrast, the Sedlis criteria, a “one size fits all” risk-based algorithm for post-hysterectomy radiation is designed to trigger a recommendation for adjuvant radiation with a combination of risk factors and only at a very high threshold of >30% recurrence risk. While this latter tool has been used by clinicians for many years, this approach lacks some nuance and may no longer be relevant for every cervical cancer subtype. Conversely, the histology-specific nomograms presented herein accurately and linearly represent risk of recurrence for both SCC and AC tumors and suggest

consideration of adjuvant radiation at lower thresholds than the Sedlis criteria. This more contemporary approach may provide a more tailored and effective tool for clinicians to base adjuvant treatment recommendations to their patients with cervical cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This study was supported by National Institute of Health grants to NRG Oncology (1 U10 CA180822) and NRG Operations (U10CA180868).

The following Gynecologic Oncology Group member institutions participated in the primary treatment studies: University of Miami School of Medicine, Wake Forest University Health Sciences, University of California Medical Center at Irvine-Orange Campus, Duke University Medical Center, University of Colorado Cancer Center – Anschulz Cancer Pavilion, University of Southern California, State University of New York Downstate Medical Center, University of Texas Southwestern Medical Center, University of Alabama at Birmingham, University of Mississippi Medical Center, Women's Cancer Center of Nevada, University of North Carolina at Chapel Hill, Walter Reed National Military Medical Center, University of Oklahoma Health Sciences Center, Oregon Health Sciences University, Rush University Medical Center, University of California at Los Angeles Health System, Abington Memorial Hospital-Asplundh Cancer Pavilion, Georgetown University Hospital, Indiana University Hospital/Melvin and Brem Simon Cancer Center, Stanford University Medical Center, Albany Medical College, University of Michigan Medical School, University of Minnesota Medical Center-Fairview, LDS Hospital, Penn State Milton S. Hershey Medical Center, University Hospital of Jacksonville, Tufts-New England Medical Center, University of Pittsburgh Cancer Institute (UPCI), Ohio State University Comprehensive Cancer Center, University of Iowa Hospitals and Clinics, University of Connecticut, University of Puerto Rico, University of Rochester Medical Center, University of Cincinnati, Washington University School of Medicine, University of Utah Medical Center, St. Louis University Medical Center, Moffitt Cancer Center and Research Institute, Gynecologic Oncology Network/Brody School of Medicine, Eastern Pennsylvania GYN/ONC Center, P.C., Medical University of South Carolina, University of Kentucky, Community Clinical Oncology Program, Fox Chase Cancer Center, Abramson Cancer Center of the University of Pennsylvania, Cooper Hospital University Medical Center, University of Virginia, Temple University School of Medicine, Cleveland Clinic Foundation, Stony Brook University Medical Center, Tacoma General Hospital, Mayo Clinic, Eastern Virginia Medical School, University of Massachusetts Memorial Health Care, University of Chicago, Thomas Jefferson University Hospital, University of Toronto/ Sunnybrook Regional Cancer Centre, Emory University Clinic, Fred Hutchinson Cancer Research Center, Johns Hopkins Oncology Center, MD Anderson Cancer Center and University of Arizona.

The findings of this manuscript were presented as a poster discussion at the ASCO Annual Meeting (virtual), in June 2020.

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RESEARCH HIGHLIGHTS

- Cervical adenocarcinoma is a distinct cervical cancer subtype; treatment should be based on data specific to this subtype.
- Risk factors for recurrence differ for squamous cell carcinoma and adenocarcinoma of the cervix.
- For adenocarcinoma of the cervix, tumor size is the risk factor associated with the highest risk of recurrence.
- For squamous cell carcinoma, depth of invasion is the risk factor associated with the highest risk of recurrence.
- Histology-specific nomograms accurately and linearly represent risk of recurrence for squamous cell and adenocarcinoma.

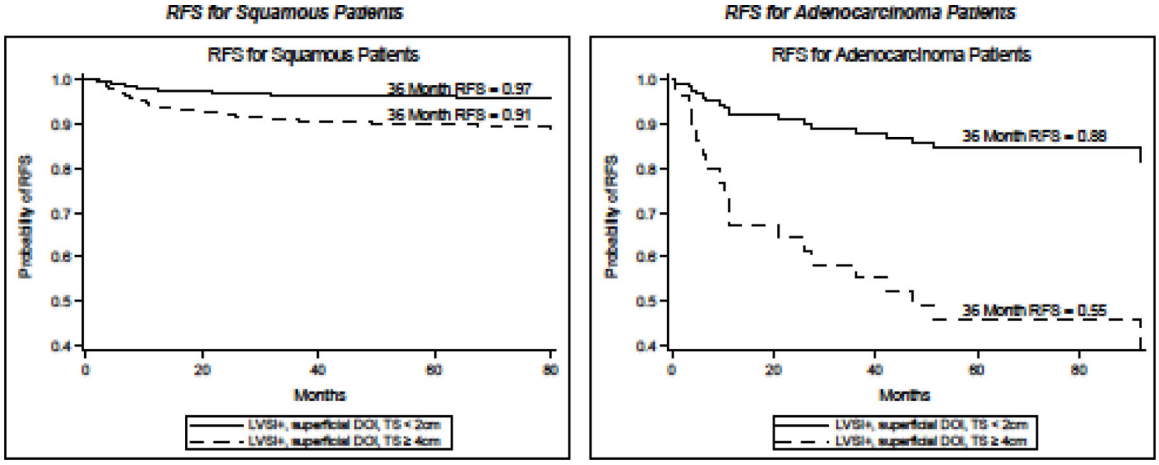

Figure 1: RFS - Positive LVSI, superficial DOI, impact of TS (SCC and AC modeled separately) (online only)

* The impact of tumor size for AC tumors is significant with a 36 mo RFS of 0.88 vs. 0.55 for TS <2cm vs. ≥4cm. Alternatively, tumor size (<2cm vs. ≥4cm) in patients with SCC does not significantly change 36 month RFS (0.97 vs. 0.91).

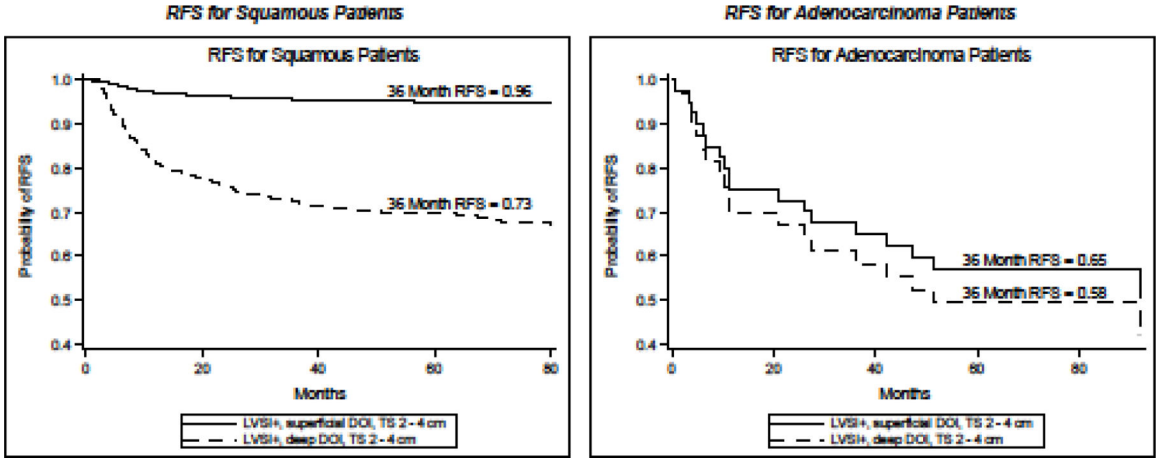

Figure 2: RFS - Positive LVSI, TS 2–4cm, impact of DOI (SCC and AC modeled separately) (online only)

* The impact of deep invasion for SCC tumors is significant with a 36 mo RFS of 0.96 vs. 0.73. Alternatively, deep invasion (compared to superficial invasion) in patients with AC does not significantly change 36 month RFS (0.65 vs. 0.58).

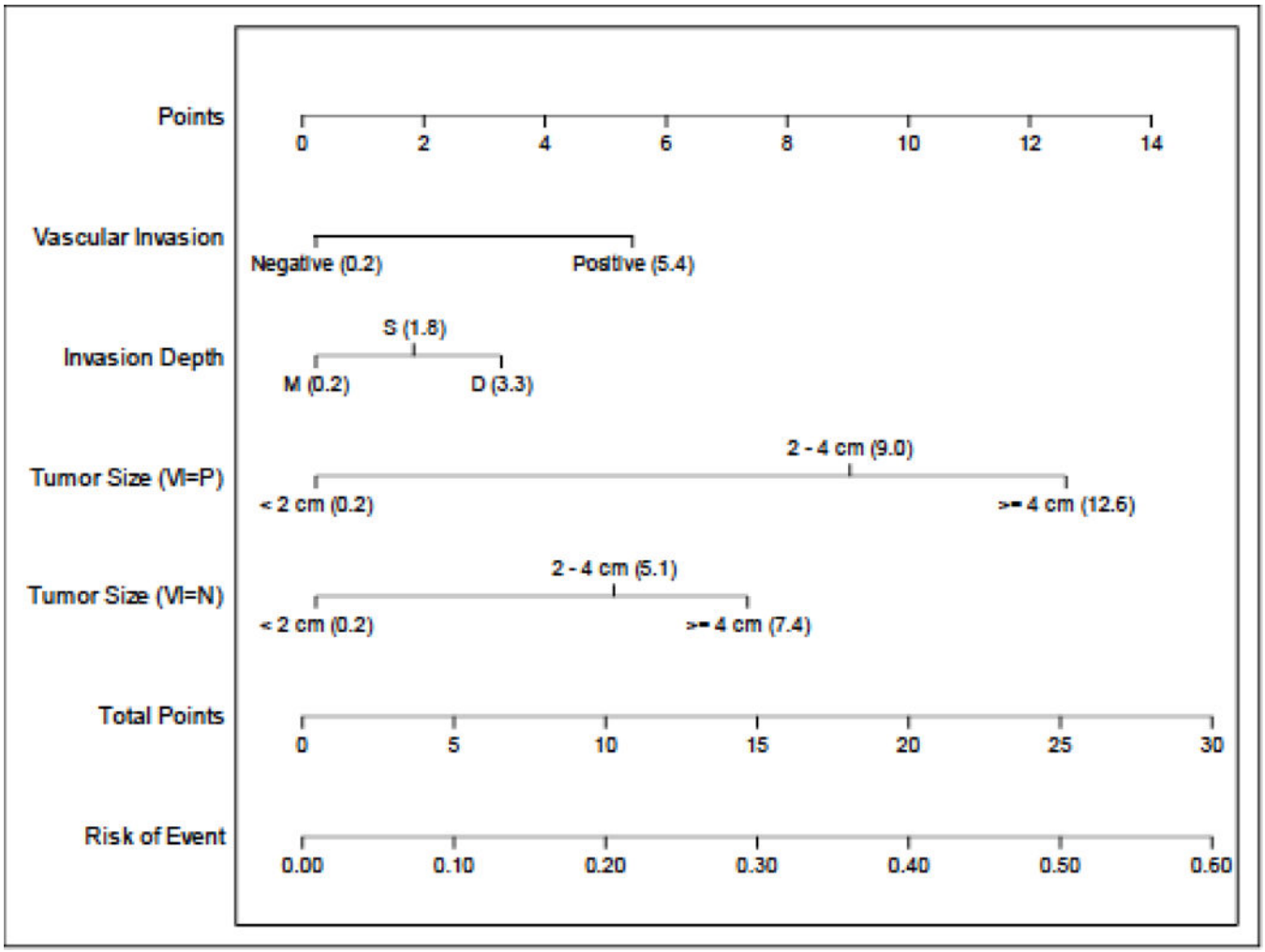

Figure 3. AC Nomogram for Recurrence

For each variable, the assigned points are provided in parentheses after the level of the variable. For example, positive LVSI assigns 5.4 points. Utilize the tumor size variable based on whether there is positive or negative lymphovascular invasion: VI =P for positive lymphovascular invasion, VI=N for negative lymphovascular invasion.

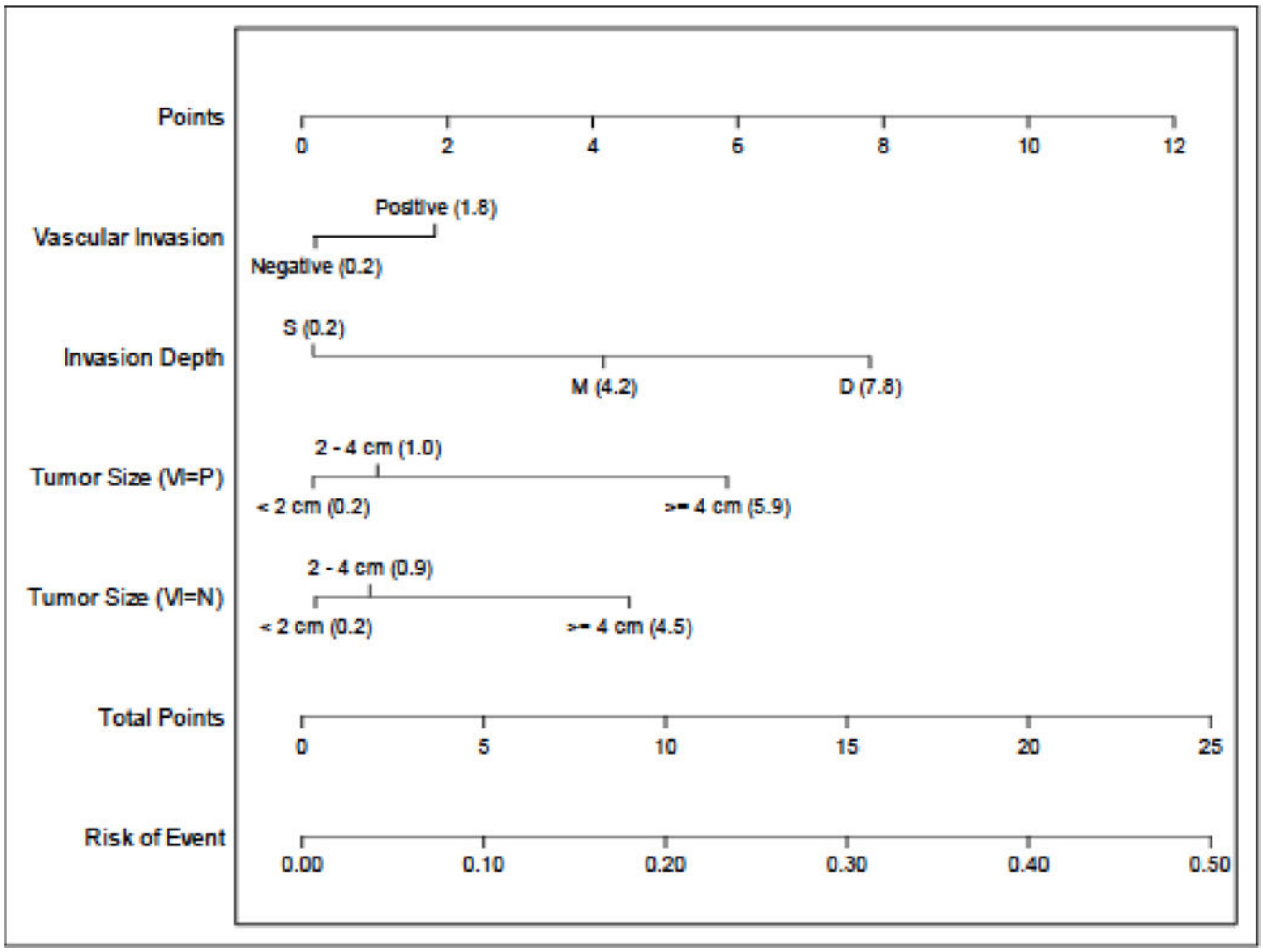

Figure 4. SCC Nomogram for Recurrence

For each variable, the assigned points are provided in parentheses after the level of the variable. For example, positive LVSI assigns 1.8 points. Utilize the tumor size variable based on whether there is positive or negative lymphovascular invasion: VI =P for positive lymphovascular invasion, VI=N for negative lymphovascular invasion.

Table 1.

Demographics and Tumor Characteristics

Variable	Squamous N=715	Adenocarcinoma N=105	P-value
Age	**N=616**	**N=95**	0.45
(years) Mean (CI)	42.3 (41.4 – 43.2)	43.3 (40.9 – 45.8)	
Race	**N=520**	**N=21**	<0.01
White	406 (78.1)	13 (61.9)	
Black	97 (18.6)	3 (14.3)	
Asian	17 (3.3)	5 (23.8)	
Performance Status	**N=715**	**N=105**	0.46
0	577 (80.7)	81 (77.1)	
1	134 (18.7)	24 (22.9)	
2	4 (0.6)	0 (0.0)	
Vascular Invasion	**N=708**	**N=105**	<0.01
Positive	293 (41.0)	25 (23.8)	
Negative	415 (58.0)	80 (76.2)	
Invasion Depth	**N=705**	**N=100**	0.10
Superficial	188 (26.3)	36 (34.3)	
Middle	249 (34.8)	35 (33.3)	
Deep	268 (37.5)	29 (27.6)	
Tumor Size	**N=715**	**N=105**	<0.01
< 2 cm	279 (39.0)	58 (55.2)	
≥ 2 cm and < 4 cm	239 (33.4)	28 (26.7)	
≥ 4 cm	197 (27.6)	19 (18.1)	
Tumor Grade	**N=699**	**N=105**	<0.01
1	85 (12.2)	42 (40.0)	
2	375 (53.6)	45 (42.9)	
3	239 (34.2)	18 (17.1)	

Table 2.

Cox Regression for Recurrence – SCC and AC

Risk Factor	Groups	SCC HR (95% CI)	AC HR (95% CI)
Depth of Invasion	Inner 1/3	ref	ref
	Middle 1/3	**4.31 (1.81–10.26)**	0.79 (0.17–3.67)
	Outer 1/3	**7.05 (2.99–16.64)**	1.26 (0.27–6.00)
Tumor Size	<2cm	ref	ref
	2–4cm	1.31 (0.79 – 2.15)	3.39 (0.94–12.24)
	>4cm	**2.67 (1.67–4.29)**	**4.69 (1.25–17.63)**
Vascular Invasion	Negative	ref	ref
	Positive	**1.58 (1.12–2.22)**	2.83 (0.97–8.27)

Table 3.

Comparison of 3yr RFS, nomogram recurrence risk, and Sedlis criteria for predictor variable combinations

Vascular Invasion	Invasion Depth	Tumor Size	SCC			AC		
			RFS (3 yr, CI)	Sedlis Criteria (+/−)	nomogram recurrence risk	RFS (3 yr, CI)	Sedlis Criteria (+/−)	nomogram recurrence risk
N	Superficial	(< 2 cm)	0.98 (0.96,1)	−	<5%	0.96 (0.90, 1.00]	−	<5%
N	Middle	(< 2 cm)	0.91 (0.87,0.95)	−	18%	0.97 (0.92, 1.00]	−	<5%
N	Deep	(< 2 cm)	0.86 (0.79,0.93)	−	32%	0.95 (0.87, 1.00]	−	6%
N	Superficial	(2–4 cm)	0.97 (0.95,1)	−	<5%	0.86 (0.70, 1.00]	−	24%
N	Middle	(2–4 cm)	0.88 (0.84,0.93)	−	22%	0.89 (0.77, 1.00]	−	20%
N	Deep	(2–4 cm)	0.82 (0.75,0.89)	−	38%	0.83 (0.66, 1.00]	−	26%
N	Superficial	(≥ 4 cm)	0.94 (0.9,0.99)	−	10%	0.81 (0.59, 1.00]	−	34%
N	Middle	(≥4 cm)	0.78 (0.7,0.86)	+	28%	0.85 (0.70, 1.00]	+	30%
N	Deep	(≥ 4 cm)	0.66 (0.58,0.75)	+	42%	0.77 (0.56, 1.00]	+	36%
Y	Superficial	(< 2 cm)	0.97 (0.94,0.99)	−	<5%	0.88 (0.71, 1.00]	−	20%
Y	Middle	(< 2 cm)	0.86 (0.8,0.92)	−	22%	0.91 (0.78, 1.00]	−	18%
Y	Deep	(< 2 cm)	0.78 (0.7,0.88)	+	38%	0.85 (0.70,1.00]	+	22%
Y	Superficial	(2–4 cm)	0.96 (0.92,1)	−	8%	0.65 (0.32, 1.00]	−	40%
Y	Middle	(2–4 cm)	0.82 (0.76,0.89)	+	26%	0.71 (0.48, 1.00]	+	38%
Y	Deep	(2–4 cm)	0.73 (0.65,0.81)	+	40%	0.58 (0.36,0.96]	+	42%
Y	Superficial	(≥ 4 cm)	0.91 (0.84,0. 99)	+	14%	0.55 (0.19, 1.00]	+	50%
Y	Middle	(≥ 4 cm)	0.67 (0.57,0.79)	+	32%	0.63 (0.37, 1.00]	+	46%
Y	Deep	(≥ 4 cm)	0.52 (0.43,0.64)	+	46%	0.47 (0.24, 0.95]	+	52%

Table 4.

3yr recurrence risk predicted by the histology specific nomogram for tumors meeting Sedlis criteria.

Sedlis intermediate risk factor combinations	**SCC Predicted 3-yr Recurrence Risk**	**AC Predicted 3-yr recurrence risk**
LVSI positive Deep 1/3 invasion Any tumor size	38%	22%
LVSI positive Middle 1/3 invasion Tumor size ≥2cm	23%	**39%**
LVSI positive Superficial 1/3 invasion Tumor size ≥5cm	18%	**45%**
LVSI negative Middle/deep 1/3 invasion Tumor size ≥4cm	28–40%	**30–38%**