Original Research

Tumor proximity to serosal surface as an independent prognostic factor in FIGO stage 1 endometrial cancer

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Objective: Determine if tumor distance from serosal surface is an independent prognostic factor for disease recurrence and survival in stage 1 endometrial cancer. *Methods*: 747 patients diagnosed with stage 1 endometrial cancer between 1984 and 2015 were identified from an institutional database. This retrospective cohort was evaluated to assess differences in tumor distance from the serosal surface, histologic subtype, histologic grade, use of adjuvant treatment, recurrence rates and overall survival. Cox proportional hazard models were used to determine if variables of interest were related to recurrence and overall survival. Concordance correlation coefficients were used to compare our model to the 2009 International Federation of Gynecology and Obstetrics (FIGO) staging. *Results*: Tumor distance from serosal surface ranged from 0 mm–21 mm. 47 (8.7%) patients experienced recurrence. Patients with tumors located 5 mm or less from the serosal surface were 2.24 times more likely to experience recurrent disease (HR 2.24, 95% CI: 1.16 to 4.31, $p = 0.02$). Concordance rates for disease recurrence were 0.573 and 0.583 for our tumor distance model compared to the 2009 FIGO staging (95% CI: 0.568 to 0.579 and 95% CI: 0.577 to 0.589). *Conclusions*: Our study demonstrates that patients with tumors located 5 mm or less from the serosal surface have a two-fold increased risk of recurrence. Concordance rates are very similar between our model and the 2009 FIGO staging suggesting comparable predictability; these rates suggest there is room for improvement in both methods to predict disease recurrence and survival.

Keywords

Tumor proximity; Independent prognostic factor; Endometrial cancer; Uterine cancer; Stage 1; Early stage; Serosal surface

1. Introduction

Endometrial cancer is the most common gynecologic malignancy among women in developed countries and the fourth most common malignancy among women in the United States [1–7]. In 2020, over 61,000 women in the US were diagnosed with endometrial cancer, and over 12,000 succumbed to their disease [2, 3, 6]. Unfortunately, the incidence and mortality rates associated with endometrial cancer have increased dramatically over the last 35 years [1, 2, 4]. From 1990 to 2010 there has been a doubling of the incidence and tripling of the mortality rate associated with endometrial cancer in the US [8]. Despite this, the 5-year survival rate for endometrial cancer remains high at approximately 81% [1, 5, 8]. This number improves further to a 5-year survival rate of 90% for patients with stage 1 disease at the time of diagnosis [5, 8]. Some patients will experience recurrence with rates as high as 20–25% based on certain characteristics including patient age, histologic grade, depth of myometrial invasion, tumor size, and lymphovascular space invasion (LVSI) [9].

Initial treatment for endometrial cancer includes total hysterectomy with bilateral salpingo-oophorectomy and surgical staging [2, 3, 10–13]. Since 1988 endometrial cancer has been surgically staged based on guidelines updated and published by the International Federation of Gynecology and Obstetrics [10, 12, 13]. In the 2009 FIGO staging, stage 1 disease is stratified based on depth of myometrial invasion quantified by less than or greater than 50% of the myometrium involved [10, 12]. Several studies have investigated risk factors predictive of disease recurrence and prognostic characteristics warranting adjuvant treatment. Both the Gynecologic Oncology Group (GOG)-99 and Post-Operative Radiation Therapy in Endometrial Carcinoma (PORTEC-1) trials stratified patients into low- or high-risk cohorts based on risk factors for disease recurrence. This stratification was used to determine the need for adjuvant treatment [14, 15]. Specifically, in GOG-99 the authors used outer third myometrial invasion as a specific risk factor for disease recurrence as opposed to using 2009 FIGO staging which stratifies patients based on less than or greater than half of the myometrium involved [14]. Another study conducted by Lutz *et al.* [16] suggested that in their small cohort, tumor proximity to the serosa was predictive of overall survival from stage 1 endometrial cancer.

The primary objective of this study is to determine if tumor proximity to the serosal surface is associated with increased risk of disease recurrence and mortality in stage 1 endometrial cancer. The secondary objective is to compare this tumor proximity model to the 2009 FIGO staging in regard to prediction of disease recurrence and mortality.

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2. Methods

2.1 Patients

All patients diagnosed with stage 1 endometrial cancer were identified from an institutional endometrial cancer (EC) database at the Medical University of South Carolina (MUSC). This institutional database is an Institutional Review Board approved, prospectively enrolling, continuous database of all patients diagnosed with endometrial cancer at MUSC beginning in 1984. Patient information including clinicopathologic data, adjuvant treatment, postoperative complications, comorbid conditions and disease outcomes are documented continuously.

Eligible patients included all patients with stage 1 disease diagnosed between January 1984 and November 2015 undergoing treatment at MUSC. Patients were excluded from analysis if pathologic reports omitted documentation of tumor depth, records lacked follow-up information, or if patients opted for non-surgical management of their disease. Documentation of myometrial invasion and total myometrial depth were recorded to the nearest millimeter (mm). Tumor distance from the serosa was defined as depth of myometrial invasion subtracted from total myometrial width on final histopathology (**Supplemental Fig. 1**). These measurements were used to stratify patients into two groups: those with tumor distance less than or equal to 5 mm from the serosa and those with tumors located greater than 5 mm from the serosal surface. The distance of 5 mm was selected for comparison to specifically address if serosal proximity was equally or more predictive than percentage of myometrial invasion. Patients with all histologic subtypes were included for analysis. Type 1 disease included patients with endometrioid histology. Type 2 disease included patients with serous, clear cell, carcinosarcoma, or multiple histologies. Adjuvant treatments were administered at the direction of the primary oncologist. Time to recurrence was defined as time from date of diagnosis to date of clinical, radiologic, or histopathological diagnosis of recurrence. If no recurrence occurred, disease free survival (DFS) was defined as time from date of diagnosis to date of death from any cause or date of last contact.

2.2 Statistical analysis

Descriptive statistics including mean, standard deviation, frequency, and percentage were calculated for both tumor groups ($\leq$5 mm from serosa and $>$5 mm from serosa). Demographic variables were compared between these two groups via two-sample *t*-tests, Chi-square tests, or Fisher's exact tests, as appropriate. The primary statistical endpoint in the institutional cohort was recurrence of disease, defined as local or distant recurrence. Cox proportional hazards regression models were used to determine if these variables of interest were related to recurrence or overall survival, identified as a secondary endpoint. An alpha level of 0.05 was considered statistically significant.

2.3 Secondary analysis

To determine the consistency with current prediction methods concordance correlation coefficients and 95% confidence intervals were calculated to determine how similar our tumor distance model is to the 2009 FIGO staging in relation to recurrence and overall survival. Statistical analysis was performed using SAS/STAT software, version 9.4 (SAS Institute, Inc., Cary, NC, USA) and RStudio vs. 1.1.383 (RStudio, PBC, Boston, MA, USA).

3. Results

3.1 Patient characteristics

Between January 1984 and November 2015, 747 women diagnosed with stage 1 endometrial cancer were identified from the MUSC EC database. Of the 747 patients, 4 lacked data on recurrence, 188 lacked documentation of tumor distance from the serosa, and 13 lacked follow-up data, leaving 542 patients included for statistical analysis. Demographic and histopathological characteristics of patients are displayed in Table 1. Of the 542 patients, 466 had tumors located greater than 5 mm from the serosa while 76 had tumors located within 5 mm of the serosal surface. The mean (SD) age was 62.3 (10.7) years. The majority were Caucasian (76%) with endometrioid type histology (76%). The average length of follow up for both groups was 4.3 years.

3.2 Recurrence & survival

At the time of analysis, 47/542 (8.7%) women had experienced disease recurrence. Of patients with tumors $\leq$5 mm from the serosa, 15.8% (12/76) experienced recurrence. Patients with tumors located greater than 5 mm from the serosa had a recurrence rate of 7.5% (35/466). The risk of recurrence is 2.24 times higher for patients with tumors located within 5 mm of the serosa compared to those with tumors $>$5 mm away (95% CI: 1.16 to 4.31, $p = 0.02$) (Fig. 1, Table 2).

At the time of analysis, 85.4% (463/542) patients were alive, without evidence of disease. 1.1% (6/542) were living with disease, 7.4% (40/542) had died without evidence of disease and 6.1% (33/542) had died with active disease. Fig. 2 demonstrates overall survival curves for patients based on tumor proximity to the serosa. Patients with tumors located 5 mm or less from the serosa had worse survival compared to patients with tumors $>$5 mm from the serosa; however, this effect was not statistically significant (HR 1.71, 95% CI: 0.98 to 2.99, $p = 0.06$, Table 2).

Of the 542 subjects analyzed, 121 (22%) received some form of adjuvant treatment; 24% (29/123) received pelvic external beam radiotherapy (EBRT), 60% (74/123) received vaginal brachytherapy (VB), and 70% (86/123) received systemic chemotherapy. Patients receiving any form of adjuvant therapy had 2.09 times higher risk of recurrence compared to those not receiving adjuvant treatment (95% CI: 1.16 to 3.76, $p = 0.01$, Fig. 3, Table 2). There was no evidence of increased risk of mortality for receiving adjuvant therapy ($p = 0.1$).

3.3 Concordance

The secondary objective of this study was to compare our tumor distance model to the 2009 FIGO staging to determine if our model similarly predicts disease outcomes. As demonstrated in Table 3, concordance between the tumor

Table 1. Baseline patient characteristics.

Total # of patients	Total patients	>5 mm from serosa	≤5 mm from serosa	*p*-value
	n = 542	n = 466	n = 76	
Age at diagnosis (mean in years)	62.3 ± 10.7	61.4 ± 10.6	67.1 ± 10.1	<0.0001
BMI at diagnosis (mean)	35.7 ± 10.5	36.3 ± 10.4	32.1 ± 10.4	0.002
Tumor size (mean in cm)	3.5 ± 2.4	3.9 ± 2.4	3.8 ± 2.6	0.2
Depth of invasion (mean in cm)	0.5 ± 0.6	0.4 ± 0.5	1.1 ± 0.8	<0.0001
Width of myometrium (mean in cm)	2.0 ± 1.6	2.1 ± 1.7	1.4 ± 0.8	<0.0001
Length of follow up (mean in years)	4.3 ± 3.4	4.3 ± 3.4	4.3 ± 3.7	0.9
Race				
White	409 (75.5%)	349 (74.9%)	60 (78.9%)	
African American	122 (22.5%)	110 (23.6%)	12 (15.8%)	0.05
Hispanic	4 (0.7%)	4 (0.9%)	0 (0.0%)	
Other	6 (1.1%)	3 (0.6%)	3 (3.9%)	
Histology				
Endometrioid	413 (76.2%)	366 (78.5%)	47 (61.8%)	
Serous	57 (10.5%)	45 (9.7%)	12 (15.8%)	
Carcinosarcoma	30 (5.5%)	24 (5.2%)	6 (7.9%)	<0.001
Clear cell	13 (2.4%)	12 (2.6%)	1 (1.3%)	
More than one	8 (1.5%)	3 (0.6%)	5 (6.6%)	
Other	21 (3.9%)	16 (3.4%)	5 (6.6%)	
FIGO stage				
IA	460 (84.9%)	436 (93.4%)	24 (31.6%)	<0.0001
IB	82 (15.1%)	30 (6.4%)	52 (68.4%)	
Adjuvant treatment				
Yes	123 (22.7%)	98 (21.0%)	25 (32.9%)	0.02
No	414 (76.4%)	364 (78.1%)	50 (65.8%)	
Not documented	5 (0.9%)	4 (0.9%)	1 (1.3%)	
Type of adjuvant treatment[+]				
Radiotherapy (EBRT)	29 (23.6%)	21 (21.4%)	8 (32.0%)	0.3
Brachytherapy (VB)	74 (60.2%)	56 (57.1%)	18 (72.0%)	0.2
Chemotherapy	86 (69.9%)	68 (69.4%)	18 (72.0%)	0.8
Location of recurrence[±]:				
Local	30 (63.8%)	23 (65.7%)	7 (58.3%)	0.7
Distant	26 (55.3%)	19 (54.3%)	7 (58.3%)	0.8
Treatment of recurrence[±]				
Surgery	13 (27.7%)	12 (34.3%)	1 (8.3%)	0.1
Radiotherapy	22 (46.8%)	15 (42.9%)	7 (58.3%)	0.4
Brachytherapy	10 (21.3%)	7 (20.0%)	3 (25.0%)	0.7
Chemotherapy	20 (42.6%)	16 (45.7%)	4 (33.3%)	0.5
Status				
NED	463 (85.4%)	403 (86.5%)	60 (78.9%)	
Alive with disease	6 (1.1%)	6 (1.3%)	0 (0.0%)	0.02
Dead without disease	40 (7.4%)	35 (7.5%)	5 (6.6%)	
Dead with disease	33 (6.1%)	22 (4.7%)	11 (14.5%)	

[+] Denominator for calculation based on total number of subjects receiving adjuvant therapy.

[±] Denominator for calculation based on total number of subjects experiencing recurrence.

distance model and FIGO staging in regard to disease recurrence was 0.573 and 0.583, respectively. Similarly, concordance between both models in regard to overall survival was 0.559 and 0.570 respectively. The similar values and overlapping confidence intervals in both implies similar predictability between the models.

4. Discussion

Our findings show that patients with stage 1 endometrial cancer and tumor proximity within 5 mm from the serosa have increased risk of disease recurrence. These patients also have increased risk of all-cause mortality, although not statistically significant. When comparing our model to the 2009 FIGO staging, both were similar in their prediction of which patients in our cohort would experience disease recurrence

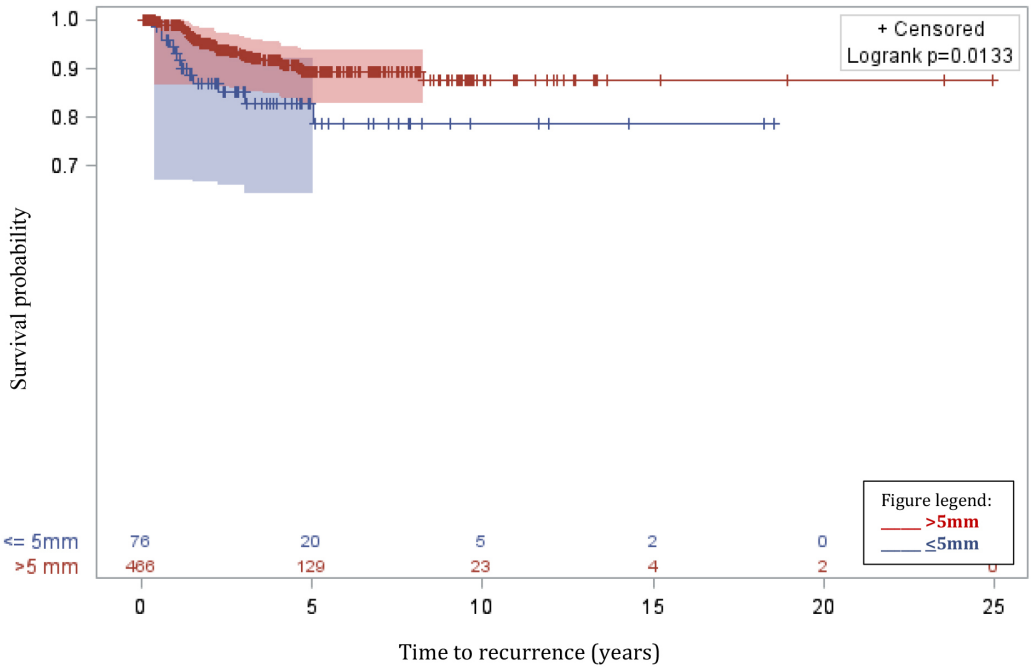

Fig. 1. Survival analysis for cancer recurrence based on tumor proximity.

Table 2. Prognostic factors affecting recurrence and survival in stage 1 endometrial cancer.

	Time to recurrence				Overall survival			
	HR	95% CI		*p*-value	HR	95% CI		*p*-value
Distance to tumor (<5 mm vs >5 mm)	2.24	1.16	4.31	*0.02**	1.71	0.98	2.99	0.06
Subtype (2 vs 1)‡	2.87	1.62	5.10	*0.0003**	2.00	1.25	3.22	*0.004**
Grade (2 vs 1)	1.70	0.75	3.86	0.2	2.02	1.08	3.80	*0.03**
Grade (3 vs 1)	4.42	2.16	9.01	*<0.0001**	3.76	2.06	6.85	*<0.0001**
Adjuvant treatment	2.09	1.16	3.76	*0.01**	1.52	0.91	2.53	0.1

‡Subtype 1 includes endometrioid histology. Subtype 2 includes serous, clear cell, and carcinosarcoma and other histology.

Table 3. Concordance between tumor distance model and FIGO staging model in terms of disease recurrence and overall survival.

	Recurrence		Overall survival	
	Concordance		Concordance	
Tumor distance model	0.573	95% CI: 0.568–0.579	0.559	95% CI: 0.554–0.564
FIGO staging model	0.583	95% CI: 0.577–0.589	0.570	95% CI: 0.565–0.575

and death.

Although patients diagnosed with stage 1 endometrial cancer have favorable prognosis and 5-year survival rates, a significant portion will experience disease recurrence. Many studies have identified prognostic factors predictive of disease recurrence and worsened survival. GOG-99 identified several of these factors including increasing age, poorly differentiated tumor grade, presence of LVSI, and outer third myometrial invasion [14]. From this, they suggested using these criteria to stratify patients into high, intermediate or low intermediate risk groups to help dictate adjuvant therapy. Since then, many randomized controlled trials have sought to identify those patients at highest risk of disease recurrence and greatest benefit of adjuvant therapy. Aside from one study conducted by Lutz *et al.* [16], no studies have been conducted to determine if tumor proximity to the serosa is an additional prognostic factor.

Since 1988, stage 1 disease has been stratified based on less than 50% or greater than 50% myometrial invasion. Our study has shown low concordance rates for the 2009 FIGO staging in predicting disease outcomes. In clinical practice, this low concordance is overcome by consideration of several other factors when selecting patients for adjuvant therapy. Although FIGO stage is noted when identifying patients at highest risk of recurrence, other clinicopathologic data are heavily weighed as well. The current National Com-

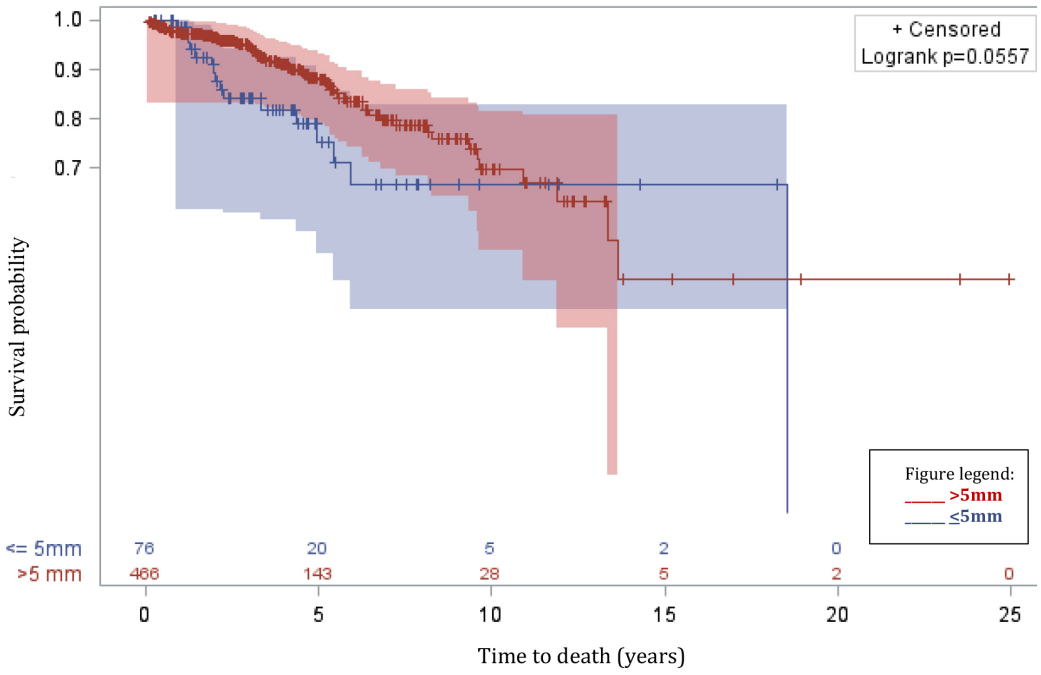

Fig. 2. Overall survival analysis of subjects based on tumor proximity.

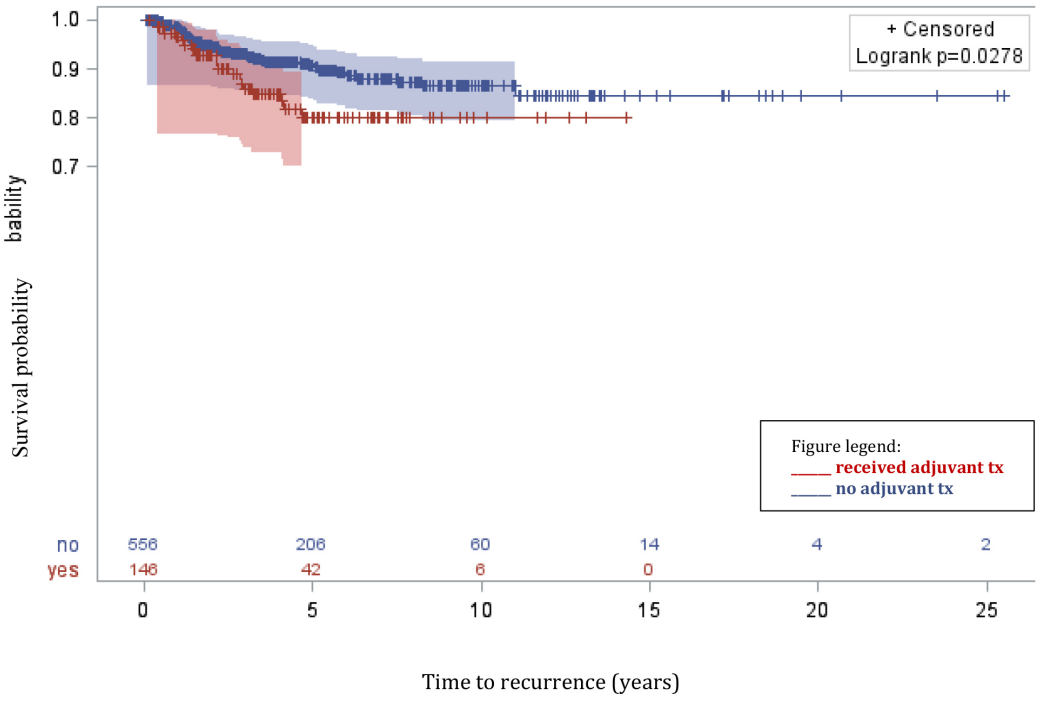

Fig. 3. Survival analysis for cancer recurrence based on whether patients received adjuvant treatment.

prehensive Cancer Network (NCCN) guidelines recommend consideration of risk factors including age, histologic grade, LVSI, and depth of invasion when selecting adjuvant treatment for stage 1 disease [17]. Our study and a similar study by Lutz *et al.* [16] suggest that tumor proximity to the serosa in addition to FIGO stage could be predictive of disease recurrence and help select those patients warranting adjuvant treatment.

There are several limitations to our study. It is a retrospective analysis, thus hindered by accurate medical records and lack of patient follow-up. The receipt of adjuvant treatment was determined by the primary oncologist, thus adding a selection and treatment bias to this analysis. Although this is a large and inclusive cohort, due to the nature of stage 1 disease there was overall low rate of recurrence and low proportion of patients with type 2 histology. Despite these limita-

tions, this study suggests an association between tumor proximity to the uterine serosa and disease recurrence in stage 1 endometrial cancer and thus warrants further examination.

The overall prognosis for stage 1 endometrial cancer is very good, but there are several tumor characteristics that dramatically increase a patient's risk of disease recurrence. This study demonstrates that tumor proximity within 5 mm of the uterine serosa is associated with increased risk of disease recurrence. We suggest notation of tumor proximity when considering adjuvant therapy for stage 1 disease and further studies to strengthen this association.

Author contributions

LMH: primary author, data collection, data analysis, manuscript author. LKB: secondary author, data collection, data analysis, manuscript editing. AEW: statistical analysis and manuscript editing. JR: data configuration, image creation. WSG: project oversight and manuscript editing. MFK: project oversight and manuscript editing. WTC: primary project oversight, data analysis, data configuration, manuscript editing. All authors have read and approved the manuscript.

Ethics approval and consent to participate

This study was conducted with Institutional Review Board approval through the Medical University of South Carolina via expedited review, ID number Pro00011754. This study was initially approved in July 2011 and has continued approval through May 2021. Subjects were consented prior to enrollment.

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Conflict of interest

The authors declare no conflict of interest. WTC is the Editorial board member of this journal, given his role as Editorial board member, WTC had no involvement in the peer-review of this article and has no access to information regarding its peer-review.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at https://ejgo.imrpress.com/EN/10.31083/j.ejgo.2021.03.2310.

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