Gynecologic Oncology 153 (2019) 74–79

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

The association between progesterone receptor expression and survival in women with adult granulosa cell tumors

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HIGHLIGHTS

- ER and PR expression was present in most granulosa cell tumors (GCT).
- High PR composite score (≥9) was associated with both decreased recurrence-free and overall survival in GCT.
- PR tumor expression was more likely in patients with diabetes.

ARTICLE INFO

Article history:
Received 20 October 2018
Received in revised form 13 January 2019
Accepted 14 January 2019
Available online 18 January 2019

Keywords:
Granulosa cell tumor
Progesterone receptor
Estrogen receptor

ABSTRACT

Background. Granulosa cell tumors (GCT) variably express estrogen receptors (ER) and progesterone receptors (PR). The goal of this study is to evaluate the relationship between ER and PR expression patterns and clinical outcomes in women with GCT.

Methods. A multicenter, retrospective analysis was performed of all cases of GCT diagnosed between 1989 and 2012. Immunohistochemical staining for ER and PR was performed on formalin-fixed paraffin embedded (FFPE) tumor tissue and interpreted using a semiquantitative scoring system that incorporated tumor cell staining proportion and intensity. Demographics, disease status, and survival information were collected. Associations between ER and PR staining scores and recurrence-free and overall survival were assessed using univariate Cox proportional hazards models.

Results. FFPE tumor blocks were available for 149/186 GCT patients. The majority of the women had clinical stage I disease (76%). ER and PR expression was present in 52% and 98% of subjects, respectively. The median composite scores of ER and PR staining were 1 (range 0–8) and 9 (range 0–15), respectively. In univariate analysis, PR composite score >9 was strongly associated with decreased recurrence-free survival (HR = 2.9, 95% CI = 1.5–5.5) and decreased overall survival (HR = 3.7, CI 1.3–10.2). ER composite score was not a significant predictor of recurrence-free survival or overall survival ($p = 0.7$, HR = 1.1, 95% CI 0.6–2.0 and $p = 0.06$, HR = 1.1, 95% CI 0.4–2.9, respectively).

Conclusions. Our results reveal that high PR composite score (≥9) was associated with both decreased recurrence-free and overall survival in patients with GCT while ER expression was not associated with survival outcomes.

1. Introduction

Adult-type granulosa cell tumors (GCT) are rare ovarian sex cord-stromal tumors, representing approximately 2–5% of all ovarian

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https://doi.org/10.1016/j.ygyno.2019.01.016
0090-8258/

malignancies [1]. The majority of GCT are diagnosed at early stage and are associated with excellent 5-year survival of 90–95%. However, advanced stage disease is associated with worse 5-year survival of 22–50% [2]. Due to the rarity of these tumors, treatment strategies are modeled after epithelial ovarian cancer (EOC) and include surgical staging and cytoreductive surgery. Granulosa cell tumors are typically indolent in nature, often with recurrences years after the initial staging surgery. Higher stage at diagnosis, residual disease after staging surgery, tumor size, nuclear atypia and increased mitotic rate have all been associated with increased risk of GCT recurrence. Given the rarity of the tumor, well-designed trials to determine the optimal adjuvant or recurrent treatment are lacking. Treatment of recurrent disease often includes a combination of hormonal agents, chemotherapy, and additional surgery depending on provider preference, the recurrence number, previous treatments, size and location of the tumor [2].

Estrogen receptors (ER) and progesterone receptors (PR) are commonly expressed in epithelial and stromal ovarian tumors. However, ER and PR expression in GCT is variable. One study of GCT ($n = 41$), identified ER and PR expression on 68% and 98% of tumors, respectively. However, diffuse PR staining was noted in 68% of GCT, while diffuse ER staining was only noted in 20% of cases [3]. A second study of GCT ($n = 56$) also demonstrated an ER negative and PR positive phenotype in a majority of GCT [4]. In primary tumors of other anatomic sites, such as breast and endometrial cancers, ER and PR testing is used to direct hormonal therapy and inform prognosis. It remains to be seen if ER and PR testing in GCT may be valuable in formulating treatment decisions and prognostication. Therefore, the objective of our study was to evaluate ER and PR expression patterns and their associations with comorbid conditions and clinical outcomes in women with GCT.

2. Materials and methods

After IRB approval, 186 subjects with the diagnosis of GCT were identified at Duke University Medical Center, Brigham and Women's Hospital, the University of Virginia, and the University of North Carolina – Chapel Hill between the years of 1989–2012. The primary objective of this retrospective study was to assess the association of ER and PR expression patterns with clinical outcomes in women diagnosed with GCT. Associations between ER and PR expression and clinicopathologic variables were also assessed. Data abstracted from the medical record included: age at diagnosis, race, body mass index (BMI), smoking status, parity, cytoreductive procedure, adjuvant therapy and type, time to recurrence, salvage treatments, and final disease status. Recurrence-free survival (RFS) was defined as the time from initial diagnosis to diagnosis of disease recurrence either by imaging or biopsy. Overall survival (OS) was defined as the time from initial diagnosis to death.

Of the 186 subjects, 149 had available paraffin blocks of GCT, including fifty (34%) from Institution 1, forty-one (28%) from Institution 2, thirty-four (23%) from Institution 3, and twenty-four (16%) from Institution 4. Immunohistochemical stains were performed through institutional specific pathology departments for estrogen and progesterone receptors. A single pathologist at each institution performed the pathologic scoring for the subjects at that site and was blinded to clinicodemographic variables. Both percentage of tumor cells staining and intensity of staining were evaluated and scored based on a historically used semi-quantitative system [3,5]. Each tumor received a score of 0–5 corresponding to no tumor staining, <5%, 6–25%, 26–50%, 51–75%, and >76%, respectively. Staining intensity scores ranged from 0 to 3 with zero for no staining, 1 for weak intensity, 2 for moderate intensity, and 3 for strong intensity. These values, for percentage and intensity, were transformed to a composite score by multiplying the points obtained from the percentage score by the points obtained from the intensity score. For example, a case with 60% of cells staining positive with strong intensity would receive a composite score of 12 ($4 \times 3 = 12$).

Descriptive statistics were summarized for patient demographics, treatment and tumor characteristics, including the mean, standard deviation and range of the continuous variables, frequency and percentage of the categorical variables. Associations between categorical variables were tested using the chi-square test. Dichotomized ER and PR composite scores and BMI were used in univariate Cox proportional hazards models to predict OS and RFS. Survival curves were generated with Kaplan-Meier estimates and groups were compared using the log-rank test. Spearman's correlation was used to show the association between ER and PR composite scores. A multivariate model including clinical variables was not performed due to limited sample size. Statistical analysis was conducted using SAS v9.4 software (SAS Institute, Inc., Cary, NC) and survival plots were created using Spotfire S+ v8.1 (TIBCO, Palo Alto, CA).

3. Results

A total of 149 patients with the diagnosis of adult-type granulosa cell tumor of the ovary who had paraffin blocks available were identified across all institutions between the years of 1989–2012 and included in this study. The mean age at the time of initial presentation was 48 years (range 12–87). With regards to race, 49% were Caucasian, 23% were African-American, 23% were unknown, 1% were Hispanic, 1% were Asian, and 1% were reported as other. Median BMI was 31 (range 16–64), with 52% of patients being obese (BMI ≥ 30). The median follow-up time was 86 months (0–468 months). Most patients presented with early stage disease (83% with Stage I, 6% with Stage II, 10% with Stage III, 1% with Stage IV) (Table 1). The majority of patients, 69%, were alive without evidence of disease at the time of data acquisition. Additionally, 9% of patients had died from their disease, 12% were alive with disease, 3% died of other disease, 2% died of unknown causes, and 5% were lost to follow-up.

Positive ER expression, defined as a composite score >0, was present in 52% of tumors and was less common than positive PR expression (98%). The ER and PR composite score results are detailed in Fig. 1. The median composite scores of ER staining was 1 (range 0–8) and the median composite score of PR staining was 9 (range 0–15). In ER positive cases, receptor staining was frequently demonstrated in a low proportion of cells, with resultant composite scores of 1 or 2 in 80% of cases (Fig. 2). In contrast, receptor staining in PR positive cases was commonly found in a high proportion of cells resulting in composite

Table 1
Demographic characteristics of study participants.

	$n = 149$[a]	%
Age (median [range] years)	48 [12, 87]	
Follow up (median mo)	86	
Race		
White	73	49.0
Black	35	23.5
Hispanic	2	1.3
Other	4	3.0
Unknown	35	23.5
BMI		
18–24.9	52	35
25–29.9	20	13
≥30	77	52
Stage		
I	94	83
II	7	6
III	11	10
IV	1	1
Unknown	36	
Institution		
1	50	33.6
2	41	27.5
3	34	22.8
4	24	16.1

[a] May not add up due to missing values.

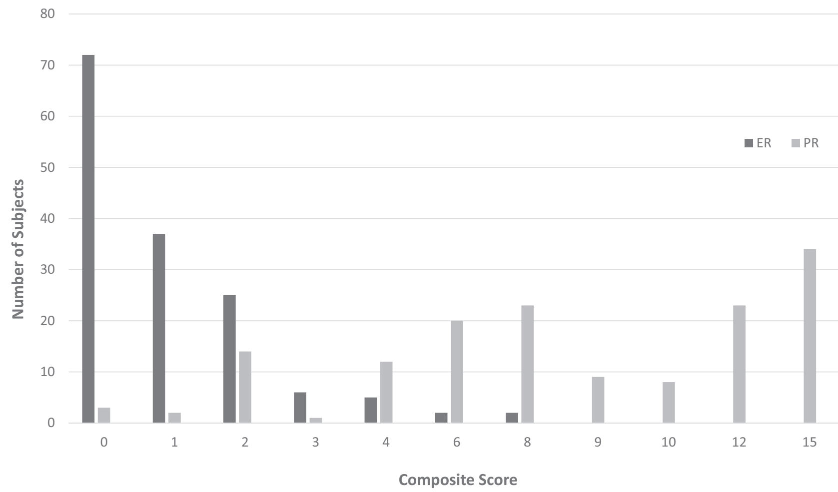

Fig. 1. Estrogen and progesterone receptor staining composite scores.

scores of 6 to 15 in 80% of cases (Fig. 2). Specifically, 39% of PR positive cases had either of the two highest possible composite scores of 12 and 15. While the overall ER and PR staining patterns were comparable at all centers, one center had significantly higher overall ER and PR scores ($p < 0.001$ and $p = 0.014$, respectively).

Associations between hormone receptor and survival outcomes were evaluated. ER composite score alone was not a significant predictor of RFS or OS ($p = 0.3$, HR = 1.4, 95% CI 0.9–1.4 and $p = 0.8$, HR = 1.0, 95% CI 0.7–1.6, respectively) (Fig. 3). In contrast, the PR composite score alone was found to be a significant predictor of both RFS and OS when modeled continuously ($p = 0.0003$, HR = 1.14, 95% CI 1.06–1.23, and $p = 0.045$, HR = 1.12, 95% CI 1.002–1.25, respectively). Specifically, high PR composite scores were associated with worse RFS and OS. When evaluated as a dichotomous variable, a PR composite score >9 yielded a three-fold increase of recurrence ($p = 0.001$, HR = 2.9, CI 1.5–5.5) and a four-fold risk of death ($p = 0.01$, HR = 3.7, CI 1.3–10.2) (Fig. 4).

On analysis of the 94 patients with Stage 1 disease, 85% ($n = 81$) received no adjuvant treatment, 13% ($n = 12$) received adjuvant chemotherapy, and 2% ($n = 2$) had an unknown adjuvant therapy status. No patient with Stage I disease received adjuvant hormonal therapy. Of the Stage I patients receiving adjuvant chemotherapy, 10 of 12 (83%) received a platinum-based regimen: bleomycin-etoposide-cisplatin in 7 patients (58%), etoposide-cisplatin in 1 patient (8%), cyclophosphamide-Adriamycin-cisplatin in 1 patient (8%), and carboplatin-paclitaxel in 1 patient (8%). Additionally, 1 patient received melphalan (8%) and 1 patient received a non-platinum-based regimen, specific type unknown (8%). The proportion of patients with Stage I disease and an ER composite score ≥1 was not significantly different than the proportion of patients with Stage II–IV disease and a composite score ≥1 (57% vs 37%,

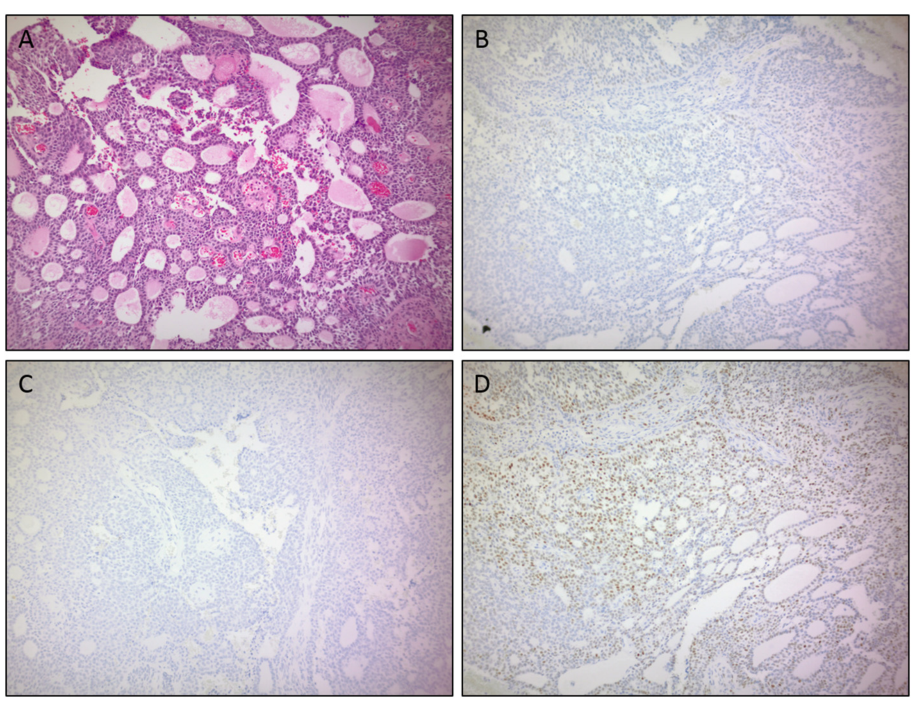

Fig. 2. Adult granulosa cell tumor (A) exhibits characteristic nuclei and Call-Exner bodies on 40× H&E (B) 10× Negative ER/PR staining control (C) 10× GCT demonstrating estrogen receptor staining with composite score of 2 (2 for proportion and 1 for intensity) (D) 10× GCT demonstrating progesterone receptor staining with composite score of 12 (4 for proportion and 3 for intensity).

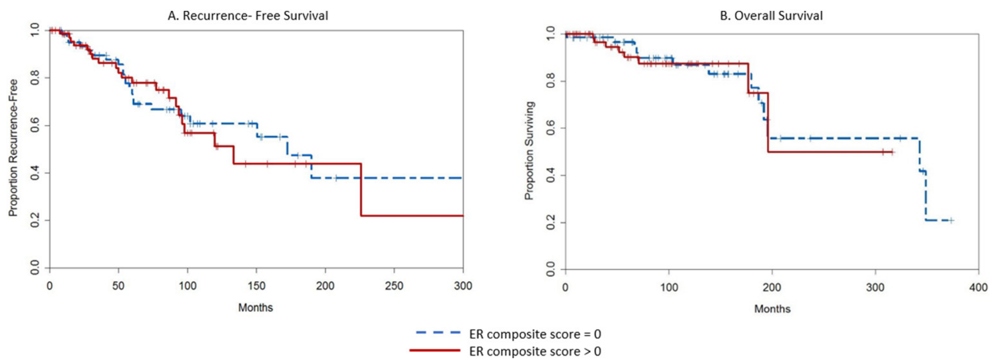

Fig. 3. Kaplan-Meier curves for ER staining for (A) recurrence-free survival and (B) overall survival.

respectively, $p = 0.10$). Similarly, the proportion of the Stage I cohort with a PR composite score of ≥9 was not significantly different than the proportion demonstrated in patients with Stage II–IV disease (50% vs 53%, respectively, $p = 0.83$). Additionally, associations between hormone receptor and survival outcomes were evaluated for the Stage I disease subset. The ER composite score was not a significant predictor of RFS or OS in the Stage I cohort ($p = 0.467$, HR = 1.54, 95% CI 0.74–3.21, and $p = 0.522$, HR 1.48, 95% CI 0.44–5.01). Within in the Stage I subset, the PR score significantly predicted survival. In patients with Stage I disease, a PR composite score ≥9 yielded a >2.5 fold increase risk of recurrence and a five-fold increase in the risk of death ($p = 0.021$, HR = 2.67, 95% CI 1.26–5.67, and $p = 0.014$, HR = 5.50, CI 1.20–25.27, respectively).

Of the 115 patients with available information regarding diabetes status, there was a significant association between PR expression and diabetes. A larger proportion of patients had diabetes in the high PR composite score group (≥9) versus those in the low PR composite score (<9) group (31% vs 14%, respectively $p = 0.029$). There is no association between ER and PR composite score expression and other clinical variables.

When evaluating the relationship between BMI and hormone receptor status, there were no significant differences in ER or PR composite scores between those in normal BMI and obese BMI categories ($p = 0.4$ and $p = 0.8$, respectively). Furthermore, BMI, when modeled as a continuous variable, was found not to be a significant predictor of recurrence-free survival (RFS) or overall survival (OS) in patients with GCT ($p = 0.6$ and $p = 0.3$, respectively). Results were similar when BMI was considered as a categorical variable.

4. Discussion

Our multicenter, retrospective study is the largest study that evaluates the association of ER and PR expression with survival outcomes in adult-type granulosa cell tumors. Previous studies have demonstrated that stage at diagnosis, presence of residual disease, size of tumor, and presence of diabetes are predictors of recurrence in patients with granulosa cell tumors [6,7]. Our data revealed that the presence of a high PR composite score, regardless of stage, is a strong predictor of both decreased recurrence-free and overall survival in patients with adult granulosa cell tumors. Additionally, we demonstrated that the ER composite score has no association with survival outcomes. Multiple reports in the literature demonstrate that PR staining is more frequent and more intense than ER staining in granulosa cell tumors [3,4,8]. This receptor expression pattern in granulosa cell tumors is consistent with the receptor expression pattern we demonstrated in our study, giving fidelity to our data despite lacking a central pathology review.

The major function of an ovarian granulosa cell is to convert androgens to estradiol through aromatase in response to follicle-stimulating hormone (FSH) during the follicular phase of the menstrual cycle. After ovulation, the luteinized-granulosa cells then produce progesterone during the luteal phase to maintain a potential pregnancy and inhibit the maturation of additional follicles [8,9]. Elevated gonadotropin levels, as seen in menopause and puberty, have been associated with granulosa cell tumorgenesis [10].

The specific role of ER and PR in adult-type GCT remains unclear. The classical PR receptor, as stained for in our study, is a steroid hormone activated nuclear receptor that is a ligand dependent transcription factor [11]. The progesterone receptor is expressed in two isoforms, PR-A and PR-B, which demonstrate distinct and overlapping transcriptional responses resulting in proliferative and anti-proliferative functions depending on the cellular and tissue context [12]. The expression of PR and PR isoforms has been demonstrated to be a valuable marker for tumor aggressiveness and disease progression in breast, endometrial and lung cancer, much like we have now demonstrated in adult-type GCT [13–15]. However, there is no single hypothesis that has been able to explain how loss and/or gain of PR expression relate to cancer development and progression, and response or resistance to endocrine therapy. For example, PR-B cells are increased in both DCIS and breast cancer, yet loss of PR expression in breast cancer is associated with

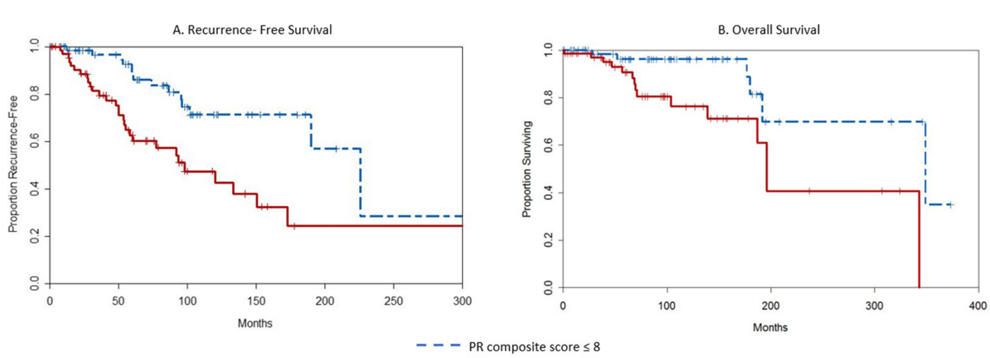

Fig. 4. Kaplan-Meier curves for PR staining for (A) recurrence-free survival and (B) overall survival.

endocrine resistance, aggressiveness and poor prognosis [16]. Further highlighting the proliferative and anti-proliferative nature of the PR, low PR expression predicts poor clinical outcomes in patients with non-small cell lung cancer, but treatment with PR antagonist improves the survival in a murine lung cancer model [15]. Adding to the complexity, is the interaction between ER and PR. Not only is the PR mediated through the ER, it has been demonstrated that progesterone-bound progesterone receptors modulate ER gene expression, often through down regulation [17]. How to translate this information to clinical practice is unknown.

Currently standard therapeutic approaches have been proposed by the National Comprehensive Cancer Network for the management of granulosa cell tumors and focus on chemotherapeutic agents as first-line options for stage II–IV disease [18]. The NCCN recommends numerous hormonal therapy options for recurrent disease including aromatase inhibitors, leuprolide, progestins, and tamoxifen. Several small clinical series and case reports evaluating the effect of these hormonal agents on GCT have demonstrated mixed efficacy [19,20]. A retrospective study reporting consecutive patients from a single institution found hormonal therapy had a pooled objective response rate of 18% in twenty-two patients [21]. In contrast, a systematic review of GCT response to hormonal therapy included 19 prospective studies, yielding 31 cases, and found a pooled overall response rate (complete and partial response) of 71% to hormonal therapy of any kind. Aromatase inhibitors demonstrated the most number of complete and partial responses (100%, $n = 9$), and medroxyprogesterone acetate (MPA) also demonstrated a 100% pooled overall response rate ($n = 3$) [22]. In the systematic review, 7 of the 31 patients had ER/PR testing and 6 of 7 demonstrated PR positive staining. Receptor staining was dichotomously reported with no information on staining diffuseness or intensity. Of the six PR positive cases, 2 patients had a complete response, 1 had a partial response, 1 had stable disease and 2 had disease progression. Given that a PR composite score was not calculated and four different treatment regimens were used for the six PR positive patients, it is difficult to draw any conclusions from the receptor staining in the systematic review [14]. Additionally, aromatase activity has been detected in 95% of ovarian tumors with progesterone receptors, making treatment with aromatase inhibitors a reasonable option in tumors identified as having a high PR composite score [23]. However, the recent prospective PARAGON phase II clinical trial of anastrozole in 41 women with hormone receptor positive GCT demonstrated a response rate of only 2.5% (one partial response). However, disease stabilization was evident with a clinical benefit rate at 12 weeks of 80%. Whether or not PR composite scores can be used to direct hormone therapy is unknown [24].

There is conflicting literature regarding the relationship between granulosa cell tumor risk and obesity. Boyce et al. demonstrated that patients with GCT were significantly more likely to be obese (BMI ≥30) (OR 5.80, 3.01–11.2). However, the study did not evaluate the association between obesity and survival outcomes [6]. Suri et al. demonstrated poor survival outcomes in diabetic women with GCT (HR 3.19, 1.08–9.44) independent of obesity status and that obesity (HR 1.38, 0.62–3.10) was not associated with granulosa cell tumor recurrence [7]. Our findings also demonstrated no association between BMI and either ER or PR receptor status, or survival outcomes. However, our findings demonstrating an association between PR expression and survival outcomes may be confounded by diabetes given that diabetes has been associated with survival outcomes and was associated with PR expression in our current study. A regression model controlling for diabetes exposure between the two groups was unable to be performed due to the small sample size. Therefore, further evaluation of obesity and diabetes is needed in larger data sets in order to fully explore the relationship between these comorbidities, hormonal status, and survival outcomes in women with granulosa cell tumors.

There are several limitations to our study including the retrospective design and inherent bias associated with these studies. In addition, the study lacked centralized pathology staining and review. One institution had a higher overall ER and PR composite scores compared to the other institutions. This could have resulted from pre-analytical variables such as cold ischemia time, age of tissue blocks, tissue fixation time, or the tissue fixative. Alternatively, analytical variables such as the antibody clone or interobserver inconsistency could have affected the results. Despite the higher proportion of ER and PR composite scores at one institution, the overall staining frequency and intensity of both ER and PR receptors in our study, among all institutions, is consistent with the published literature [3,20]. Additionally, it is unknown if the tissue samples reflect the primary tumor or recurrent disease and information regarding hormonal therapy exposure prior to tissue sampling is also unknown. ER and PR expression may change over time (primary vs recurrent disease), and be heterogeneous (primary vs metastatic disease). Hormone expression changes and heterogeneity can be mechanisms for developing resistance for endocrine therapies. Additional limitations include limited data on comorbidities, lack of uniform treatment (patients were treated by institutional and physician preference), and inability to perform a multivariate analysis due to small sample size.

Despite these limitations, this study represents the largest multicenter study of GCT evaluating the association between clinicopathologic variables and survival outcomes. Our finding regarding the association between high PR composite scores and decreased survival outcomes warrants further evaluation to confirm the prognostic association and to determine if using a high PR composite score (≥9) as a marker for hormonal therapy responsiveness may be a useful therapeutic approach in the setting of routine progesterone receptor testing in granulosa cell tumors.

Conflict of interest statement

The authors of this paper have no conflicts of interest related to this submission.

Author contributions

AMP: Contributed to data collection, data organization, and primary manuscript authorship.

JE: Contributed to hypothesis generation, study design, data collection, and manuscript editing.

AS: Contributed to hypothesis generation, study design, data collection, and manuscript editing.

JN: Contributed to data collection and manuscript editing.

SB: Significant role in reviewing of pathologic slides, pathologic hypothesis, manuscript revision and editing.

PG: Contributed to hypothesis generation, study design, and manuscript editing.

ES: Contributed to data collection and manuscript editing.

LD: Significant role in manuscript revision and editing.

GB: Responsible for statistical analysis and manuscript editing.

JE: Contributed to data collection and manuscript editing.

NH: Contributed to data collection and significant role in manuscript revision and editing.

AAS: Development of study concept and significant contributions to hypothesis generation, study design, and manuscript editing.

Acknowledgements

Duke University Department of Obstetrics and Gynecology Charles B. Hammond Research Fund.

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