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Stage I granulosa cell tumours: A management conundrum? Results of long-term follow up☆,☆☆

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HIGHLIGHTS

- Stage I granulosa cell tumours have a good prognosis but relapse can have significant morbidity.
- Surgery remains a key treatment of granulosa cell tumours at diagnosis and relapse.
- Alongside advances in our molecular understanding, improvements in novel therapies are needed.

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ABSTRACT

Optimal management of women with early stage granulosa cell tumours (GCT) presents a management conundrum — they have excellent prognosis but a third will relapse. Advances uncovering the molecular characteristics of GCT have not been matched by improvements in our understanding and treatment.

Methods. Stage I GCT patients referred to Auckland City Hospital (1955–2012) and Princess Margaret Cancer Centre (1992–2012) were identified. Baseline characteristics, histopathology and outcomes were recorded retrospectively.

Results. One hundred and sixty stage I GCT patients were identified with a median age of 49 years. Median follow-up was 7.0 years (range 0.1–44.2 years).

Fifty-one patients (32%) relapsed with a median time to relapse (TTR) of 12.0 years (1.3–17.7 years) — 20 initial relapses occurred 10 years post-diagnosis. Higher relapse rates (43% vs. 24% $p = 0.02$) and shorter TTR (10.2 vs. 16.2 years $p = 0.007$) were seen with stage Ic versus stage Ia disease. Cyst rupture was associated with increased relapse ($p = 0.03$).

Surgery was the main therapeutic modality at relapse. Eighty six percent of patients received non-surgical management at least once post-relapse. Clinical benefit rate was 43% with chemotherapy, 61% with hormonal therapy and 86% with radiation.

Five- and 10-year overall survival (OS) were 98.5 and 91.6%, respectively. Median OS was similar in patients with (24.3 years) and without relapse (22.3 years).

Conclusion. Surgery remains fundamental at diagnosis and relapse. Caution should be exercised in recommending adjuvant chemotherapy at initial diagnosis given median OS was greater than 20 years even with relapse. Hormonal therapy at relapse appears encouraging but needs further assessment. Novel treatment strategies need exploration with international collaboration essential for this.

1. Introduction

Granulosa cell tumours comprise less than five percent of ovarian malignancies and are often thought of as an indolent malignancy with a favourable prognosis [1,2]. In comparison to epithelial ovarian

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malignancies, they tend to present at an earlier stage with symptoms of oestrogen excess [3]; however, they have a tendency to late relapse with first recurrences reported as late as 37 years after initial diagnosis [4]. The relapsing remitting course can be associated with significant morbidity and difficult therapeutic quandaries.

Whilst the role of surgery is well defined in granulosa cell tumours, the role of other therapeutic modalities remains less clear [5,6]. With no randomised controlled trials, retrospective data is used for the basis of clinical therapeutic decision making in both the adjuvant and recurrent settings [7,8]. Conducting prospective studies is hindered by the limited patient population and prolonged clinical course. The therapeutic dilemma in stage I patients is further perpetuated by the lack of clearly identified prognostic factors.

Relapse rates of stage I patients have been reported to be as high as 30% in long-term case series [9]. Due to their rarity and slow growth pattern, identification and validation of prognostic factors has been difficult [10,11]. Numerous pathological and clinical factors have been postulated but stage remains the only well validated factor [3,9,10,12–14].

To evaluate this complex disease, we retrospectively reviewed patients presenting with stage I disease at two institutions with respect to clinicopathological features at presentation and correlated this with clinical outcome in an attempt to identify high risk features and assess treatment efficacy.

2. Methods

Following local ethics approval, a search for patients with adult granulosa cell tumours was performed at Princess Margaret Cancer Centre in Toronto, Canada and Auckland City Hospital in Auckland, New Zealand. One hundred and forty-eight patients were identified through the Cancer Registry at Princess Margaret Cancer Centre between 1992 and 2012, with 57 patients identified from the Auckland Regional Gynecology Multidisciplinary Team database, between 1955 and 2011. Patients with juvenile granulosa cell tumours were excluded. A retrospective, non-concurrent cohort study was performed with the two datasets combined for analysis. Time periods for each centre differed based on the individual records of each site.

Clinical and pathological information regarding age, clinical symptoms, FIGO stage, tumour size and histologic features, treatment and follow up were recorded until 30th May 2014. Data was collected from clinical notes, surgical and pathology reports and registry data. Radiological and clinical notes were used to assess response. Predefined cut-offs for mitotic rate (>4/10 high power field) were based on other series but there was significant variability between reports defining these limits. Tumour size was analyzed based on size equal to or greater than 10 cm and as a continuous variable.

A pathology review was performed on all patients at Auckland City Hospital as part of their multidisciplinary meeting. At Princess Margaret Hospital a central pathology review was not repeated.

2.1. Statistical analysis

The objectives of this study were to: (i) explore risk factors for relapse; (ii) assess the role of adjuvant therapy; and (iii) investigate the response to treatment at relapse. Response was assessed based on the radiological findings and clinical interpretation. Clinical benefit rate was defined as a complete response, partial response or stable disease for six months. Response rate was defined as a complete or partial radiological response. Confirmatory scans were not performed given the retrospective nature of this study.

Descriptive statistics were used to characterize the patient population. The clinicopathological characteristics and treatment variables were evaluated for association with relapse. Follow-up period was measured from the date of primary diagnosis to the time of last follow-up visit.

Overall survival (OS) was defined as the time from the date of initial diagnosis to the date of death of any cause. Time-to-recurrence (TTR) was defined as the time period from the date of initial diagnosis to the first observation of recurrence. Overall survival and time to relapse curves were estimated using the Kaplan–Meier method and were compared with the log-rank test. Patients were censored when lost to follow up. An exploratory analysis was performed to explore the time to relapse and overall survival in patients with at least 5 years follow up. Individual risk factors for relapse were explored in this population.

Statistical analysis was performed using the PRISM 6.01 programme (California, USA) and SAS 9.2 software. A two-sided p value <0.05 was considered statistically significant. Hazard ratios were calculated for potential risk factors for relapse.

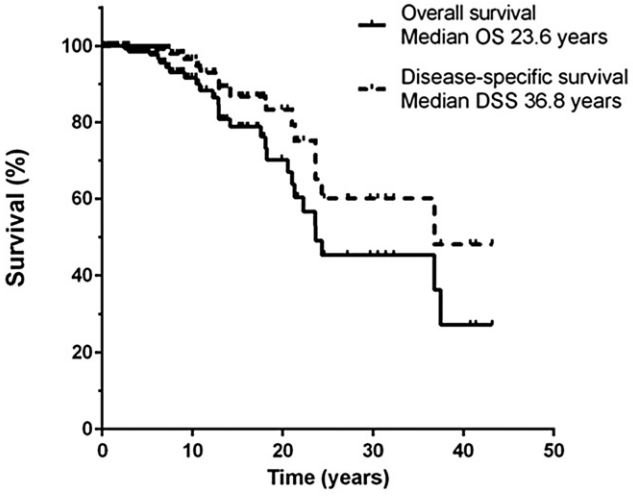
3. Results

Two hundred and five patients with adult granulosa cell tumours were identified between the two institutions of which 160 had stage I disease (78%). In total, 104 (65%) and 46 (29%) patients had stage Ia and stage Ic disease, respectively. The median age at diagnosis was 49 years (range 22 to 86 years). Mean follow up was 10.2 years (median 7.0 years; range 0.1 to 44.2 years). One hundred and seven patients (67%) had at least five years follow up.

At presentation 28 patients (18%) were nulliparous. Bleeding and abdominal pain or bloating were common presenting symptoms seen in 41% and 31%, respectively. Four patients were diagnosed during pregnancy (3%) and six (4%) during investigations for infertility. Ten patients (6%) had concomitant endometrial cancer.

Sixty-five (41%) patients had tumours equal to or larger than 10 cm. Cyst rupture was documented in 34 (21%) patients. The majority of these occurred at the time of surgery (21; 62%). Mitotic rate was not documented in over 40% of the patients reviewed. Of those where mitotic rate was documented 23 patients (26%) had a mitotic rate greater than 4 per 10 high power field (HPF).

Ninety-nine (62%) patients primarily underwent a total abdominal hysterectomy with bilateral salpingo-oophorectomy (plus/minus omentectomy, washings and lymphadenectomy), with a further 26 (16%) having planned fertility sparing surgery. Nine of the patients treated with fertility sparing surgery had stage Ic disease. Six stage I



	5 years	10 years	15 years	20 years
Overall survival (%)	98.5	91.6	78.8	70.2
Disease specific survival (%)	99.2	96.4	86.6	83.3

Fig. 1. Overall survival (OS) in stage I patients. Overall survival (median OS 23.6 years) and disease specific survival (median DSS 36.8 years).