RECURRENCE IN GRANULOSA CELL TUMOUR OF THE OVARY- A RETROSPECTIVE STUDY

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ABSTRACT

BACKGROUND

5% of all ovarian cancers are granulosa cell tumour. However, they are the most common subtype of ovarian sex-cord tumours (70%). They usually occur in young women and are usually detected at an early stage. The aim of this study was to report the clinical characteristics of GCT patients and to identify the recurrence rate.

MATERIALS AND METHODS

All cases of GCTs, treated at Caritas Cancer Institute between 2003 and 2007, were retrospectively included. Kaplan-Meier's statistical method was used to assess the relapse-free survival and the overall survival.

RESULTS

20 patients with GCT were included in the study. The mean age was 56 years (36-76 years). Patients mainly presented with abdominal mass and/or pain. Mean tumour size was 20 cms. The majority of patients had a stage I disease. Two out of three patients with stage IV disease had liver metastasis. Stage I disease and low-to-intermediate mitotic index were associated with a better prognosis in univariate analysis but were not independent prognostic factors.

CONCLUSION

This tumour has long natural history and late relapses. That's why a long active follow-up is recommended. In Indian patients, hepatic metastases were more frequent than other series. The prognosis remains good and ideal cytoreduction is an important prognostic factor.

KEYWORDS

Recurrence, Cytoreduction, Neoplasm, Granulosa Cell Tumour.

HOW TO CITE THIS ARTICLE: Joseph JV, Thomas MB, Mathew J. Recurrence in granulosa cell tumour of the ovary- a retrospective study. J. Evid. Based Med. Healthc. 2019; 6(7), 415-417. DOI: 10.18410/jebmh/2019/87

BACKGROUND

Among all malignant ovarian tumours, 5% are of germ cell origin, and account for approximately 70% of malignant sex cord-stromal tumours.[1] Granulosa cell tumours have been diagnosed from infancy through the tenth decade of life, the peak incidence being premenopausal decade. The malignant potential of these tumours is low and recurrences, are often late and found in 10-33%. Many investigators have found that age, stage, mitotic index and size of tumour to be of prognostic importance. In poor risk patients the risk for metastases even after long delay, is substantial.[2] They first were reported by Rokitansky in 1855. Although there is no consensus on the pathogenesis of these tumours, most investigators believe they originate from early ovarian mesenchymal as they are composed of granulosa cells, theca cells, and fibroblasts in different degrees.[3] Surgery is the mainstay of treatment. Combined modality treatment is considered in patients with advanced stage.[3] In this study, we aimed to describe epidemiologic factors in Indian population and the incidence of relapse and prognosis.

Financial or Other, Competing Interest: None.
Submission 25-01-2019, Peer Review 27-01-2019,
Acceptance 06-02-2019, Published 12-02-2019.
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DOI: 10.18410/jebmh/2019/87

MATERIALS AND METHODS

A retrospective study of all patients with GCT diagnosed and treated in the Surgical Oncology Department at Caritas Cancer Institute from 2003 to 2007. Quantitative variables were expressed using mean and median values. Qualitative variables are expressed as absolute and relative frequencies. Statistical analyses were performed using SPSS 20.0 software. Kaplan-Meier's statistical method was used to assess the recurrence free survival and overall survival.

RESULTS

20 women with a mean age of 56 years using (36-76 years) were included in the study. 61% of cases presented with abdominal mass and/or abdominal pain. Postmenopausal bleeding was reported in 32% of cases (). Ultrasound imaging was performed in all cases and showed mainly cystic unilateral mass (96.2%). Median tumour size was 20 cm (4-33 cm). Abnormally elevated levels of serum tumour marker CA-125 were reported in 63.8% of patients. The staging was as follows: stage I represents 70%, stage III 23.8%, and stage IV 6.2%. The primary treatment was surgery in all

cases. Intraoperative tumour rupture occurred in 5 patients. Adjuvant treatment was chemotherapy. Adjuvant chemotherapy was a platinum-based regimen: some cases needed adjuvant radiotherapy.

		%
Age	>60	76.2
	<60	23.8
Menopausal Status	Premenopausal	51.2
	postmenopausal	48.8
Symptoms at Diagnosis	Abnormal Uterine Bleeding	53.7
	Abdominal Pain	20
	Abdominal Distension	13.8
	Asymptomatic	12.5
Preoperative Endometrium	Not Assessed	46.2
	Normal	2.5
	Pathological	51.3
Preoperative CA 125	Normal	36.2
	Elevated	63.8

Table 1. Characteristics of Patients with Recurrence

		%
Ovarian Tumour	Unilateral	96.2
	Bilateral	3.8
Ascites	Present (total)	28.8
	In Stage 1	16.1
	In Stage 3-4	58.3
Initial Surgeries	Primary Staging	86.2
	Re Staging	13.8
Surgical Stages	1	70
	3	23.8
	4	6.2
Retroperitoneal Lymph Nodes	Present	8.8
	Absent	91.2
Peritoneal Spread	Present	16.2
	Absent	83.8

Table 2. Surgical and Pathological Characteristics of Patients

Initial Stage	Adjuvant Treatment	Site of Rec.	Rec. Time (Months)
4	CT & RT	Abdomen	37
1	None	Pelvis	55
3	CT &RT	Abdomen	28
1	None	Pelvis	48
3	RT	Pelvis	49
3	CT	Pelvis	40
1	CT	Abdomen	62
4	CT & RT	Abdomen	23
3	CT & RT	Abdomen	32

Table 3. Characteristics of Patients with Recurrences (All Underwent Surgery)

DISCUSSION

GCT is a very rare tumour with a known good prognosis. Since it is a rare disease, limited data are available.[3] Clinical findings of our population are comparable to the literature findings. GCTs usually occur in menopausal or postmenopausal women.

The most reported signs in the literature are abdominal pain and/or abdominal distension (30% to 50%) postmenopausal bleeding, amenorrhea, and intermenstrual bleeding.[1] The size usually reported in the literature is >10 cm (73.5%) but it can vary from a small nonpalpable lesion to large masses (3-24 cm).[4] GCT presents at early stages in 81% of cases (stage I, 71%; stage II, 10%) and at late stage in 19% of cases (stage III, 11%; stage IV, 8%).[4] in our study, the largest tumour size was 33 cm with stage III (19%) and large tumours were common in our study. Stage IV disease was comparable to literature (10%). Metastatic sites of GCTs pulmonary and skeletal metastases are uncommon; 15% of relapses occurred in retroperitoneum nodes.[5] Hepatic metastases are rare with an incidence of 5-6% of all GCT recurrences.[6] We found higher rate of hepatic metastasis compared to literature.

The mainstay of treatment is a complete surgery ideal primary cytoreduction.[4] Adjuvant chemotherapy is recommended for patients with advanced stage and recurrent disease or in high risk early stage.[5] The most used chemotherapy regimen is a BVP (bleomycin, vinblastine, and cisplatin) or a BEP regimen, which substitutes etoposide for vinblastine.[7]

The major factors suspected in a number of studies were age, tumour size, rupture of tumour, mitotic activity, nuclear atypia, aneuploidy (in 5-20% GCT), p53 overexpression, high Ki-67, and stage of the disease.[5] We noted that the disease stage was the most reported factor affecting survival in GCT patients. However, these studies are limited by their retrospective method of analysis, the small number of patients included, and the heterogeneity of the different populations. Wu et al in a large series of 100 cases of GCT reported survival rates at 5 and 10 years of 98% and 96%, respectively, for stage I and 70% and 60%, respectively, for stage II.[8] Similar data was found by Park et al with the 5-year and 10-year overall survival rates in early stage (stage I and II) disease being 99% and 90%, respectively, while in advanced stage (stages III and IV) they were 80% and 67%, respectively.[9]

Conflicting data were reported regarding the prognostic value of age, tumour size, residual disease, and tumour rupture. In fact, Ayhan et al. found that patients aged below 60 years had better mean time of survival (154.6 versus 89.2 months,).[10] Some studies showed that tumours larger than 10 cm had lower survival.[3] Thomakos et al. showed that increased tumour size by one cm was associated with 13% increase in recurrence risk. In our study, there was no impact of tumour size in recurrence (DFS at 5 years in tumour larger than 10 cm was 50% versus 65% in tumours less than 10 cm).[3]

In Ranganath et al. study, median survival of GCT patients who underwent optimal cytoreduction was 60

months in contrast to 19 months for those who did not with a decrease in survival from 82% to 22%.[11] Tumour rupture was associated with a decrease in 25-year survival from 86% in patients with stage IA disease to 60% in patients with stage IC.[5] In our study, we did not find any impact on survival of postoperative residual disease and tumour rupture. OS at 5 years in patients with residual disease was 57% versus 70% in patients with optimal cytoreduction (). In case of tumour rupture, OS at 5 years was 68% versus 76% in other cases ().

GCTs have a tendency for late recurrence. The recurrence rate in our study was 32%, whereas it was 44% in Wu et al.'s study. In this study, early relapses were significantly related to advanced stage.[8] The longest reported time to recurrence was 40 years.[4] In our study, median RFS was 8.4 years (6.8-9.9 years).

Local pelvic recurrence was reported in 70% of cases; only 9% of recurrences were abdominopelvic, 6% were retroperitoneal, 6% were pelvic and retroperitoneal, and 3% were abdominopelvic and retroperitoneal.[12] In our study, recurrences were mainly located in the pelvis (60%).

Multidisciplinary treatment approach usually consists primary cytoreduction followed by chemotherapy and in selected cases radiotherapy also may prolong the DFS.[4] Brown et al. used bevacizumab in 8 patients with recurrent GCT. The response rate was 38% and median progression-free survival was 7.2 months.[13]

CONCLUSION

Granulosa cell tumour is an uncommon ovarian neoplasm. It is known for relapse even years after a curative treatment. Hence, an active lifelong follow-up is recommended with clinical examination and tumour markers such as inhibin B.[14] Disease stage and effective primary surgery with the standard adjuvant therapy seem to be the only reliable prognostic factors.

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