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ORIGINAL ARTICLE

# Retrospective Analysis of 32 Cases of Ovarian Granulosa Cell Tumours

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## Abstract

**Introduction** Granulosa cell tumour (GCT) comprises 2–5% of ovarian malignancies. They are hormonally active tumours and may present with menstrual complaints, abdominal distension or infertility. Prognosis is generally favourable because of the early stage at diagnosis and less aggressive behaviour.

**Materials and Methods** Medical records of 32 cases presenting from January 2008 to December 2014 were retrospectively analysed for the patient characteristics, tumour characteristics and the treatment received.

**Results** The mean age was 42.75 ± 10.25 years (range: 22 to 70 years). The most common presenting symptom was abdominal distension (50.00%) followed by menstrual complaints. The mean tumour diameter was 15.24 cm (range: 4–25 cm). Endometrial pathology was found in 4 patients (12.50%), and all had simple hyperplasia without atypia. Twenty-four patients underwent primary staging surgery; one patient underwent interval debulking surgery after neo-adjuvant chemotherapy. Seven patients had undergone surgery elsewhere of which 4 underwent re-staging and three were given chemotherapy. All patients had the final histopathology of adult granulosa cell tumour except one patient with juvenile granulosa cell tumour. Most patients had stage I disease (81.25%). Post-operative chemotherapy was administered to 22 patients. The most commonly used regimen was paclitaxel and carboplatin. The overall 5-year survival rate was 90%. The mean overall survival was 36.95 ± 34.08 months (range: 0.50 to 112.00 months). Two patients had recurrence at 38 and 44 months, respectively.

**Conclusion** GCT of the ovary is a rare tumour with a tendency for late relapse. Survival is generally excellent as majority of the patients present in early stages.

**Keywords** Granulosa cell tumours · Ovarian malignancy · Sex cord–stromal tumours · Rare ovarian tumours

## Introduction

Granulosa cell tumour (GCT), described for the first time in 1855 by Rokitansky, accounts for 70% of all sex cord–stromal tumours. It comprises 2–5% of all ovarian malignancies [1]. Overall incidence is between 0.6 and 1.7 cases per hundred thousand women per year [1, 2].

GCTs can be divided into adult (95%) and juvenile types. Adult GCT occurs commonly in post-menopausal women, while the juvenile type is seen in the first three decades of life. Patients may present with abdominal distension, menstrual complaints or infertility. Fifteen per cent present with acute abdomen due to rupture and hemoperitoneum, and 10% with post-menopausal bleeding. GCTs are hormonally active and produce oestrogen, FSH, folliculin and inhibin. As a result of hyperoestrogenism, endometrial pathology occurs in 26 to 76% of patients [3, 4].

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Around 75% of GCTs are diagnosed in early stage. Complete surgical resection of the tumour is the mainstay of treatment. Adjuvant therapy has been variously described. They have a favourable prognosis as compared to epithelial ovarian cancers due to early stage at diagnosis and less aggressive behaviour. Around 25% of the patients develop recurrence, which is often delayed and may occur even after a disease-free interval of up to 6 to 23 years [5, 6].

Prospective studies are difficult due to rarity and need for long-term follow-up. The present study is a retrospective study through which we have evaluated the clinicopathological characteristics and outcome of GCTs in the series of patients treated at our institute over a period of 7 years.

## Materials and Methods

The present study is a retrospective study done in the Department of Gynaecological Oncology from January 2008 to December 2014. A total of 32 patients, diagnosed with granulosa cell tumours (GCT) during this period, were included in the study. Approval from the institutional review board was obtained. Information was recorded regarding the clinical characteristics of the tumour, including age at presentation, parity, menopausal status, symptoms, size of tumours and tumour markers (CA-125, oestradiol and inhibin B). A pre-operative biopsy from the tumour was obtained in a few cases. Histopathology was reviewed for all patients who had undergone primary surgery elsewhere.

Surgery was offered to all the patients, including those who underwent incomplete surgery elsewhere. Surgery included peritoneal washings, omentectomy, biopsy of any suspicious area and/or multiple peritoneal biopsies, total hysterectomy, bilateral salpingo-oophorectomy and complete tumour debulking. A pelvic and para-aortic lymphadenectomy was done in the earlier cases. Fertility-preserving surgery was performed in young patients desiring fertility. It involved preservation of the uterus and the opposite normal ovary. An endometrial biopsy was performed to rule out a concomitant endometrial pathology in all the patients, especially those with abnormal uterine bleeding and where uterine preservation was planned.

A record was made of the various surgeries performed, the intra-operative findings, the final histopathology report and the stage of disease. The staging system used for GCT is the same as applied for epithelial ovarian cancer. Patients with advanced stage and high-risk early cases were given post-operative adjuvant chemotherapy. One patient was also given neo-adjuvant chemotherapy followed by further chemotherapy post-surgery. Various chemotherapeutic regimes and the number of cycles given were recorded. All patients were enrolled for 3-monthly follow-up for 2 years followed by 6-monthly follow-up. During the follow-up visits, clinical and radiological evaluation was done. Tumour markers (CA-125, oestradiol and inhibin B) were monitored on each visit in patients with elevated pre-operative values.

The patients were followed up till December 2017. The site and nature of relapse and treatment offered for relapse were also noted. Kaplan–Meier survival analysis was performed to find the survival patterns. Mean overall and disease-free survival was calculated.

## Results

### Patient Characteristics

The clinical characteristics of patients with GCTs are summarised in Table 1. The age at diagnosis ranged from 22 to 70 years with a mean age of $42.75 \pm 10.25$ years. The peak incidence was in the fifth decade of life (46.88%). The majority of the women had parity of more than 3 (68.74%). Three patients were nulliparous (9.38%). Thirteen patients (40.62%) were pre-menopausal. Out of the total 19 post-menopausal patients, 4 had surgical menopause due to previous vaginal hysterectomy. The most common presenting symptom was abdominal distension in 16 patients (50.00%), followed by vaginal bleeding; post-menopausal bleeding in 9 (28.12%) and menorrhagia in 5 (15.63%) patients.

Of the 16 patients presenting with abdominal distension, 14 had large tumour size (> 10 cm). Four patients also had ascites along with large tumour size. Three of the 14 patients with menstrual complaints had endometrial abnormality in the form of simple hyperplasia.

### Tumour Characteristics

The pathological characteristics of the tumour are shown in Table 2. The tumour diameter was available for 31 patients, and the mean diameter was 15.24 cm (range: 4–25 cm). The tumour was right-sided in 20 (62.50%), left-sided in 12 (37.50%) and bilateral in none. Pre-operative CA-125 levels were available for 27 patients and were elevated in 15 (46.88%). Only one patient had CA-125 level > 500 U/ml. Pre-operative oestradiol levels were available for 15 patients (46.88%) and were > 500 pg/ml in 3 patients. Pre-operative inhibin B levels were done in 2 patients of whom one had elevated value.

Ascites was present in 11 patients (34.38%). Pre-operative cytology was obtained in 9 patients and was negative for malignant cells in all of them. Pleural effusion was present in 3 patients (9.38%) and was negative for malignant cells in all three.

Pre-operative endometrial evaluation was done in 25 patients (78.12%). Overall, endometrial pathology was found in 4 patients (12.50%). It was simple hyperplasia without atypia in all of them. There was no patient with simple

**Table 1** Distribution of demographic parameters of the patients

| Demographic parameters | Number ($n=32$) | % |
|---|---|---|
| *Age (in years)* | | |
| < 30 | 3 | 9.38 |
| 30–39 | 8 | 25.00 |
| 40–49 | 15 | 46.88 |
| 50–59 | 4 | 12.50 |
| ≥ 60 | 2 | 6.24 |
| Mean ± SD | 42.75 ± 10.25 | |
| Median | 43.00 | |
| Range | 22–70 | |
| *Menopausal status* | | |
| Yes | 19 | 59.58 |
| No | 13 | 40.62 |
| *Number of parity* | | |
| 0 | 3 | 9.38 |
| 1 | 0 | 0.00 |
| 2 | 7 | 21.88 |
| 3 | 12 | 37.50 |
| ≥ 4 | 10 | 31.24 |
| Mean ± SD | 3.06 ± 1.52 | |
| Median | 3.0 | |
| Range | 0–6 | |
| *Symptoms at first presentation* | | |
| Menorrhagia | 5 | 15.63 |
| Post-menopausal bleeding | 9 | 28.12 |
| Abdominal distension | 16 | 50.00 |
| Pain abdomen | 2 | 6.25 |

hyperplasia with atypia, complex hyperplasia or endometrial cancer.

## Treatment Characteristics

Ten patients were subjected to biopsy before planning surgery. In all these patients, pre-operative diagnosis of GCT was made except for one patient in whom the biopsy was reported as poorly differentiated sex cord tumour.

Table 3 shows the treatment offered to the patients. Twenty-nine patients underwent surgical procedures at our institute. Of these, 24 patients underwent primary staging surgery. One patient with advanced disease underwent interval debulking surgery after 4 cycles of neo-adjuvant chemotherapy. Four of the 6 patients, referred to us after incomplete surgery elsewhere, underwent completion/staging surgery at our institute. The 2 patients who refused completion surgery were given chemotherapy. One patient had undergone complete staging elsewhere and was referred for adjuvant therapy.

Total hysterectomy with removal of both tubes and ovaries was done in all cases, except in three women desiring

**Table 2** Distribution of clinicopathological and histopathological characteristics of the patients

| Characteristics | Number ($n=32$) | % |
|---|---|---|
| *Size ($n=31$) of tumour (in cm)* | | |
| < 10 | 6 | 19.75 |
| 10–19 | 16 | 51.61 |
| ≥ 20 | 9 | 29.03 |
| Mean ± SD | 15.24 ± 6.53 | |
| Median | 14 | |
| Range | 4–25 | |
| *Laterality* | | |
| Right | 20 | 62.50 |
| Left | 12 | 37.50 |
| Bilateral | 0 | 0.00 |
| *CA 125* | | |
| Normal | 12 | 37.50 |
| Elevated | 15 | 46.88 |
| Not measured | 5 | 15.62 |
| *Ascites* | | |
| Yes | 11 | 34.38 |
| No | 21 | 65.62 |
| *Pleural effusion* | | |
| Yes | 3 | 9.38 |
| No | 29 | 90.62 |
| *Endometrial status ($n=32$)* | | |
| Normal | 28 | 87.50 |
| Simple hyperplasia without atypia | 4 | 12.50 |
| Other endometrial abnormalities | 0 | 0.0 |
| *Capsule invasion ($n=30$)* | | |
| Yes | 5 | 16.67 |
| No | 25 | 83.33 |
| *Peritoneal cytology ($n=30$)* | | |
| Negative | 30 | 100.00 |
| Positive | 0 | 0.0 |
| *Rupture ($n=30$)* | | |
| No | 23 | 76.67 |
| During operation | 4 | 13.33 |
| Ruptured state | 3 | 10.00 |
| *Residual lesion ($n=30$)* | | |
| No | 28 | 93.34 |
| 2 cm | 1 | 3.33 |
| > 2 cm | 1 | 3.33 |
| *Lymphovascular invasion ($n=18$)* | | |
| Yes | 0 | 0.00 |
| No | 18 | 100.00 |
| *Mitosis ($n=30$)* | | |
| High | 3 | 10.00 |
| Low | 27 | 90.00 |
| *Grade of disease ($n=29$)* | | |
| 1 | 18 | 62.07 |
| 2 | 1 | 3.45 |
| 3 | 10 | 34.48 |

fertility, who underwent fertility-preserving staging surgery. All patients had infracolic omentectomy done. Ipsilateral and bilateral pelvic lymphadenectomy was done in 11 and 14 patients, respectively. In all of them, the lymph nodes were uninvolved. In one patient, an enlarged para-aortic node was excised and was found to be involved by metastasis.

The histopathological findings are shown in Table 2. Peritoneal cytology was obtained in all the patients operated at our institute. Overall, peritoneal cytology report was available for 30 patients and was negative for malignant cells in all. Information regarding tumour rupture was available in 30 patients. Seven (23.33%) of these patients had tumour rupture; 4 intra-operative and 3 pre-operative rupture. Information regarding capsular status was available in 30 patients, of which 5 (16.67%) had evidence of capsular invasion.

All patients had the final histopathology of adult GCT except one patient with juvenile GCT. Lymphovascular invasion was documented in 18 patients and was negative in all. Information about the mitotic rate was available in 30 patients. Mitotic figures of ≥ 5/10 high power field or above were interpreted as high mitotic rates. High mitosis was seen in 3 patients (10.00%). The grading of disease was available in 29 patients. Majority had grade 1 disease (62.07%). To confirm the diagnosis, immunohistochemistry was requested in 11 patients. It stained positive for vimentin in all, for inhibin in 8, for AE1 and CD99 in 2 patients each and one case each stained positive for NSE, actin and CAL.

Table 4 shows the stage-wise distribution of the disease along with survival. Majority of the patients had stage I disease (26 patients, 81.25%).

Complete resection was achieved in all, except two patients. One of these underwent staging surgery elsewhere

**Table 3** Distribution of cancer-directed treatments of the patients

| Cancer-directed treatments | Number ($n=32$) | % |
|---|---|---|
| *Treatment modality* | | |
| Surgery only | 10 | 31.25 |
| Surgery + chemotherapy | 22 | 68.75 |
| *Surgical methods underwent* | | |
| Fertility-sparing surgery | 3 | 9.38 |
| Non-fertility-sparing surgery | 29 | 90.62 |
| *Characteristics of surgery* | | |
| Incomplete surgery outside followed by staging surgery at our institute | 4 | 12.50 |
| Incomplete surgery outside followed by chemotherapy | 2 | 6.24 |
| Complete surgery outside followed by chemotherapy at our institute | 1 | 3.13 |
| Primary staging surgery | 24 | 75.00 |
| Chemotherapy followed by interval debulking surgery | 1 | 3.13 |

**Table 4** Stage-wise distribution of the cases and survival

| Stage | Number ($n=32$) | % | Mean disease-free survival ± SD (months) | Mean overall survival (months) | Median survival (months) | Status at last follow-up |
|---|---|---|---|---|---|---|
| I A | 19 | 59.37 | 26.34 ± 30.64 | 26.34 ± 30.64 | 13 | All disease free |
| I B | 0 | 0.00 | – | – | – | – |
| I C | 7 | 21.87 | 65 ± 33.60 | 65 ± 33.60 | 58 | All disease free |
| II A | 0 | 0.00 | – | – | – | – |
| II B | 1 | 3.13 | 44 | 47 | – | Associated with disease |
| III A | 0 | 0.00 | – | – | – | – |
| III B | 1 | 3.13 | 05 | 05 | – | Disease free |
| III C | 1 | 3.13 | 52 | 52 | – | Disease free |
| IV A | 0 | 0.00 | – | – | – | – |
| IV B | 1 | 3.13 | 38 | 85 | – | Associated with disease |
| Un-staged/stage could not be assessed | 2 | 6.24 | 19 ± 19.80 | 19 ± 19.80 | 19 | Both disease free |

and was referred for adjuvant therapy. She had stage IVB, grade 3 disease and residual disease of > 2 cm size. She received 6 cycles of cisplatin and cyclophosphamide at our institute. She recurred at 38 months after surgery. Radiology revealed solid-cystic lesions in the peritoneum and mesentery and a retroperitoneal mass of 12 × 14 cm size. She received multiple chemotherapeutic agents, and her last follow-up was at 85 months. The second patient had undergone interval surgery after four cycles of neo-adjuvant chemotherapy with carboplatin and paclitaxel. She had stage IIB, grade 3 disease and a residual lesion of 2 cm size, as its removal needed bowel resection for which the patient did not consent. She received two more cycles of adjuvant chemotherapy and was well till 44 months when she had a recurrence. She presented with a 10 cm mass in left iliac fossa and was started on chemotherapy with carboplatin and paclitaxel.

Post-operative chemotherapy was administered to 22 patients. Table 5 shows the various chemotherapy regimens and the number of cycles of each.

**Table 5** Distribution of chemotherapeutic regimes

| First-line chemotherapy regimen | Number of cycles | Number ($n=32$) | % |
|---|---|---|---|
| *Treated with chemotherapy* | | | |
| Yes | – | 22 | 68.75 |
| No | – | 10 | 31.25 |
| *Chemotherapeutic regimes (n = 22)* | | | |
| Carboplatin and paclitaxel | 3/4/6 | 11 | 50.00 |
| Single agent carboplatin | 5 | 1 | 4.55 |
| Cisplatin and cyclophosphamide | 5/6 | 2 | 9.09 |
| Bleomycin, etoposide and cisplatin | 3/4 | 5 | 22.73 |
| EP etoposide and cisplatin | 6 | 2 | 9.09 |
| CE etoposide and carboplatin | 6 | 1 | 4.54 |

Kaplan–Meier survival analysis was performed to obtain the survival patterns (Fig. 1). The overall 5-year survival rate was 90%. The mean overall survival was 36.95 ± 34.08 months (range: 0.50 to 112.00 months), and the median was 33.50 months. All, except the above-mentioned two patients, were disease-free. The mean disease-free survival was 35.01 ± 33.98 months. The stage-wise survival is shown in Table 4. Sixteen patients were under follow-up for 3 years. None of them had evidence of disease. Of these, seven patients were following up beyond 5 years. All, except one, were free of disease.

## Discussion

Granulosa cell tumours (GCT) are a rare group of hormonally active stromal cell neoplasms, distinguished by their ability to secrete sex steroids. They were first described by Rokitansky, in 1855, according to their appearance near the granulosa cells of the ovarian follicles.

Adult GCTs have peak prevalence in patients aged 50–55 years. In the present study, maximum patients were in the fifth decade of life. The juvenile type of GCT is usually seen in the first three decades of life. However, in our study, the only patient of juvenile GCT was 45 years old.

The patient may be asymptomatic or may present with abdominal pain (30–50%), abdominal distension or menstrual complaints [5]. Menstrual problems such as menometrorrhagia, post-menopausal bleeding or amenorrhoea occur due to prolonged exposure to tumour-derived oestrogen. With such complaints, the patient presents early, leading to diagnosis in stage I in majority of cases. In the present study, 43.75% patients were diagnosed due to menstrual abnormalities and all of these patients except one were in stage I. GCT is a vascular tumour and

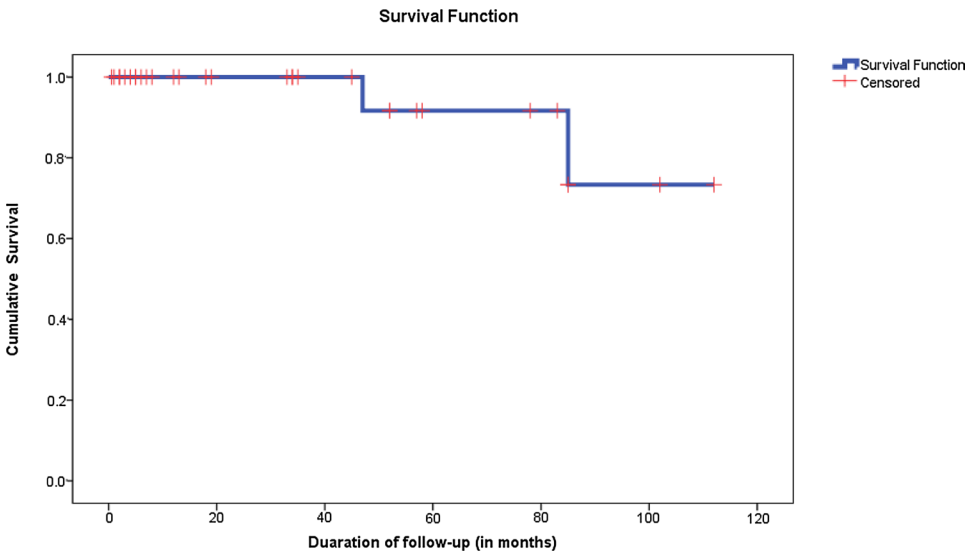


**Fig. 1** Kaplan–Meier survival curve for overall survival of the patients. The mean overall survival (mean ± SD) of the patients was 36.95 ± 34.08 months with range of 0.50–112.00 months, and the median was 33.50 months. The mean disease-free survival (mean ± SD) of the patients was 35.01 ± 33.98 months

known to rupture pre-operatively leading to hemoperitoneum, abdominal pain and hypotension. It may, thus, present acutely, mimicking an ectopic pregnancy in young patients.

Oestrogen secretion also explains why the GCTs are frequently associated with endometrial abnormalities. Endometrial hyperplasia is seen in 4–10% and endometrial adenocarcinoma in 5–35% [5]. In our study, 12.50% of patients had simple hyperplasia. Therefore, as a part of the management workup, all patients with GCTs should be subjected to a thorough endometrial evaluation, especially if fertility preservation is being considered.

The serum tumour markers are oestradiol, inhibin B and anti-Müllerian hormone (AMH). CA-125 is not correlated with the tumour progression [7]. Both serum inhibin B and AMH may be correlated with the tumour mass. However, a combination of AMH and inhibin B improves detection of recurrent disease [8].

The mainstay of treatment is complete surgery (hysterectomy, bilateral salpingo-oophorectomy) with staging for early stage and debulking surgery for advanced stage or recurrent disease [9]. As GCTs are unilateral in around 96.2% cases [3], fertility preservation can be offered to women planning pregnancy. In our series also, none of the women had gross and/or microscopic disease in the contralateral ovary. Three women underwent fertility-preserving surgery in our centre, during the study period. All three of them were disease-free at their last follow-up, the mean of which is 13.8 months. Data regarding conception are not available as the patients were lost to follow-up.

Lymphadenectomy or lymph node biopsy is now not considered necessary due to the rarity of lymph node metastasis with this tumour [10]. It has not been reported to be of prognostic value [11]. In our series, pelvic lymphadenectomy was done in the earlier cases. Of the 25 patients who underwent ipsilateral/bilateral pelvic lymphadenectomy, none had lymph node metastasis. However, in one patient with an enlarged para-aortic node, excision was done and the node was found to be involved by metastasis. Therefore, decision to omit lymphadenectomy should be taken with caution.

The diagnosis of GCT is confirmed by immunohistochemical analyses. The main immunohistochemical markers expressed by these cells are vimentin, CD 99 and alpha inhibin [4, 12]. Same was observed in the present study.

Present opinion concerning adjuvant treatment is divided. It is usually recommended for adult GCT in advanced cases as well as in high-risk, early-stage patients [1, 13]. Factors associated with early-stage GCTs, suggesting the need for adjuvant therapy, include large tumour size, stage IC, poorly differentiated histology, high mitotic index and tumour rupture [14]. In our series, out of the 26 patients in stage I, 16 received adjuvant chemotherapy. Of these, 7 patients had stage IC disease, 4 had poorly differentiated histology, 4 had large tumour size and 1 had high mitosis. Commonly used chemotherapy regimen is a BVP (bleomycin, vinblastine and cisplatin) or a BEP regimen (bleomycin, etoposide and cisplatin). Other regimes (paclitaxel + carboplatin, cisplatin + cyclophosphamide, carboplatin + etoposide) have also been variously used [15]. In our institute, the most commonly used regimen was paclitaxel + carboplatin followed by BEP.

In this study, the mean overall survival was $36.95 \pm 34.08$ months (range: 0.50–112.00 months) and the median was 33.50 months. In the present study, the overall 5-year survival rate was 90%. It may be due to many patients being lost to follow-up, as noted in our institute. Also the cause of death in such patients cannot be elucidated, due to the same reason. Wu et al. [16] reported survival rates at 5 years and 10 years as 98% and 96%, respectively, for stage I and 70% and 60%, respectively, for stage II. Thus, the most important prognostic variable is the stage of the disease. The recurrence rate is also related to the stage. Ahyan's study revealed recurrence rates of 5.4%, 21% and 40% for stage I, stage II and stage III, respectively [3]. Adult GCTs can have late recurrences detected even up to 40 years after the initial diagnosis [17]. Pelvis is the most common site of recurrence. Therefore, lifelong follow-up is needed even in early-stage GCTs. Prolonged surveillance with tumour markers (inhibin B/AMH) and serial physical examination is reasonable.

Macroscopic residual disease after surgery is reported to be a significant prognostic factor [12]. The same has been observed in the present study. Both of our patients who developed recurrences had macroscopic residual disease after surgery. Other prognostic factors include larger tumour size, especially > 10 cm [18]. The mitotic index and lymphovascular invasion are also independent prognostic factors [19].

## Conclusion

Granulosa cell tumours of the ovary are rare tumours with a tendency for late relapses. Survival is generally excellent as majority of the patients present in early stages. Prospective studies are needed to clearly understand the clinical course of the disease and to provide adequate treatment guidelines.

### Compliance with Ethical Standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical Approval** This is an analysis of records over 7 years, approved by the institute research board and ethical committee.

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