# PROMISING OUTCOMES OF EXTRACRANIAL GERM CELL TUMORS IN CHILDREN & ADOLESCENTS: LESSONS LEARNT OVER A DECADE.

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**Abstract**

Background: The purpose of this single-centre study was to analyse the outcomes of extracranial germ cell tumors (GCTs) in children treated on a multi-modality regimen at a single-centre. Methods: Retrospective study of children (<18 years) with a histopathologically confirmed diagnosis of extracranial GCT over a period of 10 years (January'09-December'18) treated on a uniform institution-based protocol. All completely excised teratomas and stage I gonadal tumors received no further therapy (low risk); Stage IV Ovarian, Stage III-IV extragonadal GCTs received 6 cycles of chemotherapy (high risk) and the remaining received 4 cycles of chemotherapy (intermediate risk). Results: A total of 336 kids were treated of which the analysable cohort comprised of 297with a boy-girl ratio of 1.72:1 and median age of 4 years. Gonadal GCTs(n-180) were commoner than extragonadal GCTs(n-117) with ovary as primary site in 128 children(43%) and sacrococcygeal site being the commonest extragonadal location(n-41;14%). LR, IR and HR disease were noted in 60(20.2%) patients, 125(42%)patients and 112(37.8%)patients respectively. Forty-one patients relapsed and 43 children expired (disease related-33; toxic deaths-9; unknown-1). The 5-year EFS/OS was 79.3%/84.4% respectively with gonadal site, low-risk and non-metastatic disease associated with statistically better EFS (median follow-up:52.1±37.3 months). Conclusion(s): Both cisplatin and carboplatin based regimens had comparable outcomes. The low and intermediate GCTs had an excellent outcome, thus warranting a gradual shift in the approach to these tumors by reducing therapy and decreasing late effects of therapy. In high risk GCTs however, intensifying therapies to improve outcomes must be balanced against the risk of cumulative toxicity.

*Main Text:*

## PROMISING OUTCOMES OF EXTRACRANIAL GERM CELL TUMORS IN CHILDREN & ADOLESCENTS: LESSONS LEARNT OVER A DECADE.

## INTRODUCTION:

Germ Cell Tumors (GCT) are a rare, heterogeneous group of benign and malignant tumours, occurring in gonadal and midline extragonadal sites. These tumors account for an overall 3% of paediatric cancers[1]. GCTs show a bimodal distribution, with one peak in infancy and the other in adolescence[2,3]. With the advent of platinum-based chemotherapy in the 1980s, survival has improved dramatically[4]; with survival in stage I GCT approaching 100%[5].A recent hospital based cancer registry (HBCR)reported an incidence of 1.6-3.6%/0.8-4.5% in boys/girls amongst all childhood cancers[6]. A cross-sectional study from the authors' centre reports the incidence of GCTs to be 4.2% across all paediatric cancers[7,8].

The purpose of this single-centre study was to analyse the clinico-pathological outcomes and prognostic variables amongst extracranial GCTs in children and adolescents treated on a multi-disciplinary approach on standard chemotherapy regimens across a decade at a tertiary referral centre in India.

## PATIENTS AND METHODS

*Eligibility Criteria & Pre-treatment evaluation*

We analysed hospital records of all children less than 18 years with a histopathologically confirmed diagnosis of extracranial GCT over a period of 10 years (January 2009 to December 2018), who were treated on a uniform institution-based protocol at the Tata Memorial Hospital, Mumbai, India. Children who received prior chemotherapy or radiotherapy were excluded. However, children who were operated outside and received adjuvant therapy at our centre were included in the analysis (Figure 1).

Pre-treatment evaluation of all children included complete clinical examination with complete blood count, serum electrolytes, renal and liver function tests, lactate dehydrogenase and tumor markers including serum AFP and beta-HCG. While the cut-off for beta-HCG elevation was taken as 5mIU/L, AFP was deemed elevated if it was more than 5 times the mean level for that age[9]. Staging imaging consisted of Magnetic Resonance Imaging (MRI)/Computed tomography (CT) of the local site and contrast CT scan of the chest and liver.

Surgical resection was attempted upfront if feasible. In the event of significant surgical morbidity or tumors deemed unresectable, children underwent delayed surgery after 2-4 cycles of neo-adjuvant chemotherapy. Tissue diagnosis at baseline was obtained in children who underwent either a primary surgical resection or a diagnostic biopsy (especially in non-secretory GCTs). Patients who presented with elevated tumor markers with suggestive imaging findings did not undergo an upfront biopsy, and diagnosis in this subset was established post-surgery. Staging of the tumors according to the primary anatomical site was done prior to starting treatment as per COG Staging[10].

All testicular tumors underwent resection by way of high inguinal orchiectomy. A trans-scrotal biopsy however warranted a completion orchiectomy following upstaging to Stage II. Children with RPLN (retroperitoneal lymph node) of size $>$ 1cm on baseline imaging and RPLN$<$1cm coupled with persistence of elevated AFP (post orchiectomy) were stratified as Stage III. The decision of RPLN dissection was taken on a case-to-case basis and not routine. Ovarian tumors were operated and staged as per COG guidelines[11]. Ascitic fluid was collected for cytological examination and in the absence of the former, intraoperative peritoneal washings were sent. While the decision of primary surgical resection in extragonadal tumors depended on the site and discretion of the treating surgeon, the usual practice was to perform a delayed resection after 2-4 cycles of neo-adjuvant chemotherapy unless it was radiologically consistent with teratoma. In sacrococcygeal tumors, resection of the tumor with coccygectomy was the procedure of choice. In large intrapelvic tumors/retroperitoneal tumors sometimes presenting with obstructive uropathy, neoadjuvant chemotherapy followed by definitive resection until after four chemotherapy cycles, was the preferred plan**.** A similar approach was followed for mediastinal tumors too, via a median sternotomy or lateral thoracotomy.

The following pre-specified variables were collected from the cohort: demographic data, radiological and biochemical parameters for diagnosis including tumor markers, stage and risk of the disease, primary and adjuvant therapies, chemotherapy regimen and complications during treatment and outcome.

*The study was approved by the institutional ethics committee.*

*Therapy*

Written informed consent was obtained from all children or their guardians prior to instituting therapy. All patients were risk stratified after initial investigations and underwent surgery, chemotherapy or a combination of both. The risk stratification and treatment schema is shown in Figure 2. The chemotherapy regimen that was employed was PEb, consisting of Inj.Bleomycin (15 IU/m2) on day 1, Inj. Etoposide (100mg/m2) and Inj. Cisplatin (20mg/m2) on day 1-5, given every 21 days. Completely excised teratomas and stage I

gonadal GCTs did not receive any additional therapy and were kept under observation only. Patients with intermediate risk tumors received 4 cycles of PEb following surgical excision, whereas high-risk patients received 6 cycles. In children with underlying renal dysfunction or obstructive uropathy, Carboplatin (560mg/m2; AUC 7.5) instead of Cisplatin was administered with no modification in doses of the other 2 agents. After normalization of renal dysfunction,patients were switched back to Cisplatin-based regimen on the physician's discretion.

*Assessment of chemotherapy related toxicity*

All children had periodic complete blood counts to monitor hematologic toxicities. Renal function was assessed by monitoring of renal function tests (BUN/Creatinine) and Tc99-DTPA scintigraphy scan (GFR scan) done only in children who had deranged renal function tests. Brainstem Evoked Response Audiometry (BERA) in young infants and Pure Tone Audiometry (PTA) in older children monitored audiological status, wherever possible. Once in remission after completion of treatment, tumor markers were done three monthly for the first 12 months, 4 monthly for the next 12 months, 6 monthly in the third year and annually thereafter. Imaging was only done to look for relapse was done in symptomatic patients or if tumor markers were elevated on surveillance. Patients with normal tumor markers at presentation (non-secretory GCTs) had periodic regional imaging during follow-up.

*Statistical Methods*

The cohort was evaluated for both event free survival (EFS) and overall survival(OS). EFS was measured from the date of commencing therapy until the date of the occurrence of the first event, which was designated as relapse or progression or death. If no event occurred, then the date of the last follow-up was used as a censored observation. OS was measured from the date of registration until the date of death. In surviving patients, the date of the last follow-up was used as a censored observation. For survival analysis, all patients were censored at the date of last follow-up OR date of telephonic contact as on 25$^{th}$ May 2020.

EFS and OS were computed using Kaplan-Meier analysis. Statistical significance of possible prognostic factors was compared using log-rank test. Multivariate analysis using Cox proportional hazards model was performed to identify risk factors and a risk model. IBM SPSS® Statistics ver. 26 was used to compute all statistical data.

## RESULTS

*Clinical characteristics:* A total of 336 children were treated, of which 39 patients were excluded in view of prior chemotherapy before presentation. The median age of the analysable cohort (n-297) was 4 years (1.4 months – 16.6 years), with a bimodal age distribution and female: male ratio of 1.72:1 (Figure 3). Forty-three patients (14.5%) had pure teratomas (27 mature; 16 immature) of which 25 were in extragonadal sites. All pure teratomas were with surgery alone followed by observation.

Table 1 summarises the patient demographic and clinical characteristics of patients with malignant GCTs (n-254). Gonadal GCTs were more common than extragonadal tumors with ovary being the primary site in 128 children (43%) and testis in 52 children (17.5%). While testicular and extragonadal tumors were more common in children<3 years (82.6% and 77.7% respectively), ovarian tumors were seen in a higher proportion in children>11 years (61%). Metastatic disease was noted in 75 patients (25.3%) with lungs being the commonest site (Isolated-41; in combination-10). Non-pulmonary visceral metastases (NPVM) were seen in the remaining patients, of which liver was the most common site (Isolated-14; in combination-12). Pre-chemotherapy histopathological subtype was available in 253 (85%) cases, of which yolk sac tumor was the commonest (109/253; 43%). In the remaining patients, the tumor was presumptively treated as germ cell tumor based on imaging and elevated TM, and histology was established post-chemotherapy as residual teratomas. Amongst all yolk sac tumors (n-151), AFP was uniformly elevated with a median value of 16839 IU/mL (99-856496 IU/mL). AFP upwards of 1000 IU/mL was seen in 129 patients (85%).

1. *Risk grouping and treatment received:* As per the institutional risk stratification, the study cohort consisted of 60 (20.2%) low-risk patients, 125 (42.5%) intermediate-risk patients and 112 (37.7%) high-

risk patients. The cohort of malignant GCT (Table 1b) also displayed a similar risk distribution. On applying the recently drafted MaGIC risk stratification (excluding Stage I tumors, dysgerminomas and chemo-naïve teratomas were excluded)[12] to the same cohort, 136 (71%), 31 (16%) and 25 (13%) had Standard risk 1, Standard risk 2 and High risk tumors respectively. Amongst the malignant GCTs, 231/254 patients received chemotherapy; PEb regimen in 181 patients (71.2%) and JEb regimen in 27 patients (10.6%). Twenty-three patients received carboplatin in the first two cycles and completed their remainder of cycles on PEb.

2. *Outcomes and Prognostic Variables:* The 5-year EFS and OS of the entire cohort at a median follow-up of 52.1 ± 37.3 months was 79.30% and 84.40% respectively. The 5-year EFS and OS of malignant GCTs at a median follow-up of 51.9 ± 38 months was 72.50% and 82.70% respectively. Figure 4 shows the group-wise Kaplan-Meier curves of malignant GCTs in a single panel. These outcomes were compared with known prognostic variables like gender, age brackets, pre-treatment AFP level, site, stage & risk grouping of the primary tumor. Chemotherapy regimen and the MaGIC risk stratification were two additional variables compared in the subset of malignant GCTs.

On univariate analysis, gonadal sites, low risk tumors and non-metastatic tumors were associated with better EFS and OS, which was statistically significant ($p<0.05$). Amongst the malignant GCTs (n-254), low risk and standard risk 2 groups had a better OS compared to other groups. In addition, the type of chemotherapy regimen (PEb or JEb) did not have any impact on EFS or OS. However, a small proportion of patients who received the hybrid regimen had unfavourable outcome. Table 2 shows the survival outcomes against the known prognostic variables. On multivariate analysis, Stage IV GCT had an inferior EFS (RR: 2.96; 95% CI: 1.24 - 7.08; p=0.015) and OS (RR: 19.93; 95% CI: 2.46 - 161.25; p=0.005). Additionally, extragonadal GCTs had a poor EFS (RR: 1.98; 95% CI: 1.20 - 3.29; p=0.007) and OS (RR: 3.09; 85% CI: 1.65 - 5.79; $p<0.001$). The aforementioned prognostic variables failed to retain their prognostic significance when computed for, in the subset of malignant GCT. Children who received hybrid regimen had an inferior OS (RR: 2.86; 95% CI: 1.30 - 6.29; p=0.009). Age, gender and baseline AFP did not have any bearing on EFS or OS in either subsets. The demographic and survival correlates of individual group of malignant GCTs is described below:*3a. Ovarian GCTs:* One hundred and fourteen patients were eligible, of which 55 (48.2%) underwent surgery prior to presentation. Lack of thorough surgical steps, including failure to collect peritoneal washings/ascitic fluid for cytology led to upstaging in 41 patients (75%) in this subset. Twelve patients relapsed. At a median follow-up of 54 ± 38.27 months, the 5 year EFS and OS at a median follow up of 52.5 ± 32.1 months was found to be 85.9% and 90.3% respectively.*3b. Testicular GCTs:*Forty-eight patients were eligible for analysis. Thirty-five (73%) patients underwent surgery outside, of which 23 (47.9%) underwent high inguinal orchiectomy. Adjuvant chemotherapy was needed in 30 patients. Seven patients relapsed (2 in Stage I; 1 each in Stage II & III; 3 in Stage IV). At a median follow-up of 52.82 ± 39.3 months, the 5-year EFS/OS was 82.3%/91.7%. Patients who underwent surgery/biopsy prior to presentation had an inferior EFS, but this association was not statistically significant (79.5% v/s 90.9%; p=0.388).*3c. Extragonadal GCTs:*Amongst the extragonadal GCTs (n-92), sacrococcygeal tumors were the commonest (41; 44.6%) followed by retroperitoneum (14; 15.2%), mediastinum (15; 16.3%) and pelvis (5; 5.4%). A small minority of patients had GCTs in other locations (n-17; 18.5%) like vagina, maxilla, orbit and the parapharynx. While 53 (57.6%) patients were treatment-naive, 23 (25%) underwent surgical resection and 16 (17.4%) underwent biopsy prior to presentation. Eighteen patients with intra-abdominal GCTs (sixsacrococcygeal, eightpelvic and four retroperitoneal) presented with features of obstructive uropathy of varying severity, necessitating urgent procedural intervention in four of them (ureteral stenting in 2 and nephrostomy in 2 patient). Eighteen patients (19.5%) received JEb instead of PEb because of underlying renal dysfunction. Additionally, 14 patients (15.2%) received JEb for the first two cycles before continuing on PEb. Two patients had involvement of the sacral nerve plexus with neurogenic bladder and one of them had long-standing neurological complications including clubfoot. The 5-yr-EFS and OS of extragonadal tumors at a median follow-up of 45.9 ± 36.1 months was 69.0% & 70.7% respectively.

1. *Events:* During the study period amongst all GCTs (n-297), there were a total of 41 relapses and 6 progressions. The median time to relapse was 8.9 months (3.32 - 71.56 months), with 22 (53.7%)

patients, 8 (19.5%) patients and 11 (26.8%) patients having local, metastatic and combined relapses respectively. A total of 43 children died during the entire study period (disease related – 31; sepsis related – 7; suspected bleomycin toxicity – 1; unknown – 1). There were no cases of second malignant neoplasm in our cohort. Twenty-two patients (7.4%) were lost to follow-up at various time-points: 6 patients (2%) during primary therapy; 13 patients (4.4%) after completion of therapy but unavailable for contact; 2 patients (0.7%) at first relapse and 1 patient (0.3%) at second relapse. Outcomes and prognostic variables concerning relapsed/refractory GCTs will be discussed elsewhere.

2. *Toxicity of chemotherapy regimen:* As per the chemotherapy regimen, the frequency of various toxicities is tabulated in Table 3. While Grade 1/2 anaemia was more common with PEb regimen (p=0.002), grade 3/4 neutropenia and thrombocytopenia of all grades were common in JEb regimen (p=0.006; p<0.001 respectively). Audiogram reports were available in 102 patients (PEb-86; JEb-16). In the PEb cohort, Chang 1a and 1b ototoxicity was present in six (7%) and seven patients (8%) patients respectively. None of the patients on JEb had deafness. While the proportion of fatal septic episodes was more in the JEb arm, the difference was not statistically significant (10% v/s 3.96%; p=0.24). Bleomycin related pulmonary toxicity led to one death in the entire cohort.

## DISCUSSION

Ever since Einhorn[4] in his seminal paper elucidated the role of multi-agent chemotherapy in germ cell tumors in adults, it has formed the basis of treatment across all age groups. The above regimen has been employed to paediatric GCTs albeit with modifications[13], owing to concerns about cumulative toxicities if given at the same schedule as in adults. Precise comparison of outcomes in paediatric GCTs treated on multimodality regimens across various trials has been fraught with challenges because of its inherent heterogeneity, relative rarity and lack of uniform risk stratification across major study groups[10]. In resource-limited countries, these tribulations are further compounded by factors like flawed surgical approach in inexperienced centres leading to imprecise staging, late presentation, significant attrition rate, and higher incidence of sepsis-related deaths.

This retrospective study is an attempt to highlight the highly favourable outcome of germ cell tumors especially in low and intermediate risk groups treated at our centre. Our series showed an overall bimodal distribution of tumors with a female preponderance which is consistent with previous experiences[1,2]. This trend is secondary to higher incidence of ovarian tumors as compared to testicular tumors in the adolescent age group. Extragonadal tumors, especially those arising from mediastinum, however showed a male predominance similar to that in earlier studies[3]. In literature[1,13,14], extragonadal tumors have been shown to be of slightly higher prevalence as compared to gonadal counterparts because of inclusion of intracranial GCTs as an extragonadal site. The occurrence of extracranial-extragonadal GCTs was otherwise similar to that in our cohort.

Notwithstanding the necessarily adaptive nature of our risk stratification (Figure2), the outcomes of our cohort parallels the results of similar studies[11,13,15,16]. Gonadal tumors had a better outcome as compared to extragonadal tumors. Amongst ovarian GCTs, inability to ensure strict compliance to the surgery guidelines can result in incomplete staging in up to 57% patients[17]. Nearly 75% patients in patients who were operated prior to presentation were upstaged to stage III as a suitable compromise because of incomplete surgical details.

Testicular tumors had an excellent outcome irrespective of the stage. The adherence to high inguinal orchiectomy and diligent monitoring of tumor marker trend post-operatively cannot be overemphasized in this group as stage I tumors require only surgery. Several limitations exist in extrapolating this approach to LMICs like lack of accurate tumor marker measurement at presentation, inappropriate primary surgery often at a non-oncological centre and non-compliant follow-up during observation period. Nearly 3/4th of orchiectomies in our cohort were performed prior to presentation of which only half were HIO. While there was no statistically significant survival difference of because of this flawed surgical approach, an Indian study in adult GCTs has reported scrotal orchiectomy to be an adverse prognostic factor in testicular GCT[18]. Several investigators in the United States, Germany, France and United Kingdom report a similar outcome in testicular GCTs irrespective of the stage[13,19-21].

Extragonadal tumors across all sites were found to be associated with relatively dismal EFS, which was statistically significant on univariate analysis (p<0.001) and a trend towards statistical significance was noted on multivariate analysis (p–0.07). Baranzelli et al in a study classifying all extragonadal tumors as high risk demonstrated a 43% 3-year failure-free survival and 77% overall survival rate, treated on a protocol comprising of alternating cycles of Cyclophosphamide-Dactinomycin and Vinblastine-Bleomycin-Etoposide[22]. Recently, the outcomes of 165 extragonadal tumors treated on a more contemporary protocol showed a 5-year EFS and OS as 79.0% and 83.4%,respectively with age [?] 12 years and mediastinal site tumors being poor prognostic variables[16]. The superior EFS of extragonadal tumors in the said cohort can be imputed to the usage of high dose PEB in nearly half of the patients. Outcome of sacrococcygeal tumors treated on a German Trial MAKEI 83/86[23]with total cumulative doses of cisplatin and etoposide comparable to the former study[15], cite a 5-year EFS of 76% with a better outcome in tumors with delayed but complete tumor resection. Considering that the above chemotherapy regimens[15,23]come with their share of significant toxicities, extending these regimens to developing countries to achieve similar outcomes would be a challenge. A high background prevalence of malnutrition and higher incidence of both rectal carriage and bloodstream infection with multi-drug resistant organisms are hurdles specific to LMIC countries, that prevent this extrapolation[24,25]. Furthermore, dose intensification of chemotherapeutic agents that has been described in phase I/II studies to improve outcomes in high risk GCTs may not have the same applicability in LMIC populations[26].

Prognostic variables used for adult GCTs do not hold the same pertinence in children on account of differences in histology, primary site and age distribution[27,28]. With an attempt to risk stratify malignant extracranial paediatric GCTs, the Malignant Germ Cell Tumor International Collaborative (MaGIC) did a recent meta-analysis on seven GCT trials, which identified age [?] 12 years, ovarian stage IV disease and extragonadal stage III to IV disease as conferring a significantly worse prognosis[29]. Elevated levels of pre-treatment AFP level, initially reckoned to be a poor prognostic indicator was not linked to inferior outcome in this meta-analysis[22,30]. On implementing the MaGIC risk stratification to our cohort of malignant GCTs (n=192)[29], we found that the SR-1 (Standard Risk – 1) subset had an unexpectedly inferior survival compared to SR-2 (Standard Risk – 2). While all the 31 patients in SR-2 had ovarian GCT and none had extragonadal GCT, 78/136 (57.4%) SR-1 patients had tumors in extragonadal sites. Though this association was not statistically significant, we presume that a higher frequency of unfavourable site tumors adversely influenced the survival in SR-1. The lack of association of age in our cohort could also be due to fewer numbers of patients aged over 11 years in our study.

Both PEb and JEb regimens in our cohort was reasonably tolerated with a toxicity profile akin to published studies[15,21,23]. There was no survival difference between the two regimens in our cohort as is reported in literature[31]. A few patients, in whom hybrid regimen (PEb and JEb) was employed, had worse outcomes. This could be attributed to the use of this hybrid regimen in a relatively morbid cohort (extragonadal GCTs or large ovarian GCTs with obstructive uropathy at presentation). Nonetheless, as outcomes were similar on both JEb and PEb, we believe switching between either regimen midway during treatment may not be a worthwhile strategy. While the incidence of anaemia was higher in PEb regimen, the incidence of neutropenia and thrombocytopenia was expectedly higher in JEb. The incidence of myelosuppression and septic episodes noted in an Indian study was substantially less, probably because of a longer cycle interval (28 days) and a higher neutrophil count cut-off to administer chemotherapy[32]. Protocols employing carboplatin in lieu of cisplatin had a higher incidence of non-fatal haematological toxicity but ototoxicity, pulmonary toxicity and nephrotoxicity were rare[21]. One child had fatal bleomycin toxicity suggesting that although rare, even 1 day of bleomycin in the regimen can be detrimental. Overt oto-toxicity or nephrotoxicity was not found in any child, which could partly be attributable to inconsistent gathering of data on audiograms of all children and lack of a methodical long-term follow-up. Despite the overall promising outcomes of GCTs in a resource-limited centre like ours, we do understand the limitations that come with a retrospective study and relatively less number of adolescent patients. A systematic study encompassing long-term effects would be more capable of unmasking the ostensibly absent nephrotoxicity, pulmonary toxicity and the frequency of second malignant neoplasms.

## CONCLUSIONS

Our cohort demonstrates the real-world outcome of GCTs treated at a developing country with emphasis on challenges that come along with it. The low and intermediate risk tumors had an excellent outcome, thus warranting a gradual shift in the approach to these tumors by reducing therapy and decreasing late effects of therapy. In high risk GCTs however, intensifying therapies to improve outcomes must be balanced against the risk of toxic deaths and cumulative toxicity.

**CONFLICTS OF INTEREST:** None

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**LEGEND:**

Table 1. Clinico-pathological features of pediatric malignant GCTs (n-254)

Table 2. Survival figures in pediatric GCTs

Table 3. Toxicity profile of chemotherapy regimen

Figure 1. Flowchart demonstrating distribution of eligible patients.

Figure 2. Treatment schema of pediatric germ cell tumors.

Figure 3. Population pyramid of the study cohort.

Figure 4. Event free survival and overall survival of malignant germ cell tumors (n-254)

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