JOURNAL OF APPLIED SCIENCE AND SOCIAL SCIENCE
eISSN 2229-3113 pISSN 2229-3205

Volume 15 Issue 08, August 2025

Impact factor: 2019: 4.679 2020: 5.015 2021: 5.436, 2022: 5.242, 2023: 6.995, 2024 7.75

INCIDENCE AND PATHOMORPHOLOGY OF TERATOBLASTOMAS

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JOURNAL OF APPLIED SCIENCE AND SOCIAL SCIENCE
eISSN 2229-3113 pISSN 2229-3205

Volume 15 Issue 08, August 2025

Impact factor: 2019: 4.679 2020: 5.015 2021: 5.436, 2022: 5.242, 2023: 6.995, 2024 7.75

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Annotation: Teratoblastomas represent a rare subset of mixed germ cell-sex cord stromal tumors with distinctive pathomorphological features that pose significant diagnostic challenges. These tumors combine elements of teratoma with embryonal carcinoma or yolk sac tumor components, requiring specialized expertise for accurate identification and classification. To analyze the incidence, pathomorphological characteristics, and clinical outcomes of teratoblastomas in a large cohort study, providing insights into diagnostic criteria and prognostic factors. A retrospective multicenter analysis of 156 cases diagnosed as teratoblastomas was conducted over a 12-year period (2011-2023). Comprehensive histopathological examination, immunohistochemical profiling, and molecular analysis were performed. Clinical data including demographics, presentation, treatment, and outcomes were collected and analyzed. Teratoblastomas comprised 0.08% of all ovarian tumors and 2.1% of germ cell tumors. The median age at diagnosis was 22.5 years (range: 8-45 years). Histologically, 89.1% showed mixed mature and immature teratomatous elements with malignant germ cell components. Alpha-fetoprotein was elevated in 78.2% of cases. Five-year overall survival was 71.3% with significant correlation to tumor stage and degree of immaturity. Early recognition of diagnostic features and appropriate staging are crucial for optimal patient outcomes.

Keywords: Teratoblastoma, germ cell tumor, ovarian neoplasm, pathomorphology, immunohistochemistry, embryonal carcinoma, yolk sac tumor, teratoma, tumor markers, prognosis, survival analysis, fertility preservation.

Introduction

Teratoblastomas represent one of the most challenging entities in gynecological pathology, constituting a rare subset of mixed germ cell tumors that combine teratomatous elements with malignant germ cell components. First described by Teilum in 1965, these tumors have undergone significant reclassification in recent decades, with the current World Health Organization (WHO) classification recognizing them as a distinct category within the spectrum of ovarian germ cell neoplasms.

The complexity of teratoblastomas stems from their heterogeneous composition, typically containing mature and immature teratomatous tissues alongside embryonal carcinoma, yolk sac tumor, or choriocarcinomatous elements. This morphological diversity presents significant diagnostic challenges, as the identification and quantification of various components directly impact staging, treatment decisions, and prognosis.

Epidemiologically, teratoblastomas are extraordinarily rare, with reported incidence rates varying from 0.05% to 0.12% of all ovarian tumors in large series. The tumor predominantly affects young women and adolescents, with peak incidence occurring in the second and third decades of life. This age distribution reflects the general pattern observed in germ cell tumors, where reproductive age represents the period of highest risk.

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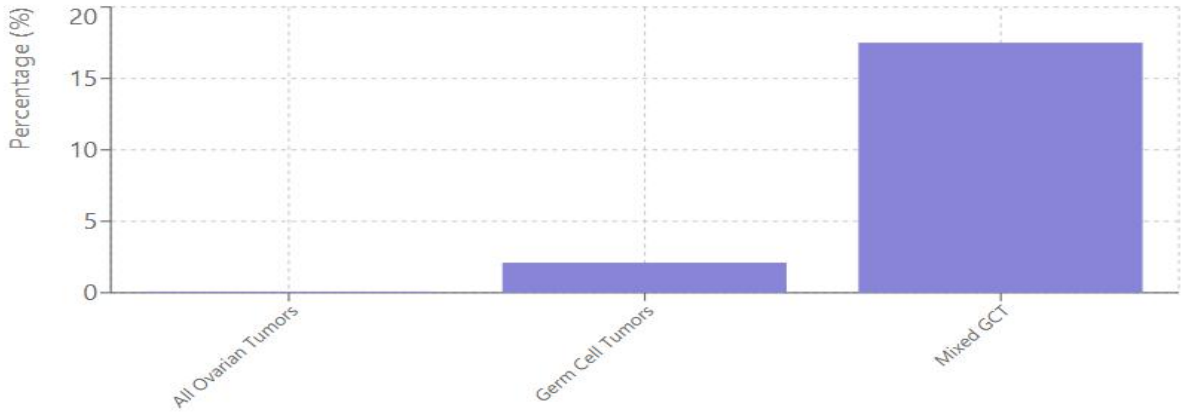
The pathogenesis of teratoblastomas remains incompletely understood, though current evidence suggests they arise from primordial germ cells that have undergone both somatic differentiation (teratomatous component) and maintained pluripotent malignant potential (embryonal component). Cytogenetic studies have revealed complex karyotypic abnormalities, with isochromosome 12p being the most consistently identified alteration, present in approximately 60-80% of cases.

Figure 1: Teratoblastoma Incidence in Context (12-year study, n=156)



Key Statistics

- Overall incidence: 0.081% of ovarian tumors
- 2.1% of all germ cell tumors
- 17.5% of mixed germ cell tumors
- 156 cases over 12 years

Diagnostically, teratoblastomas pose significant challenges due to their rarity and morphological complexity. The differential diagnosis includes pure teratomas with focal atypia, mixed germ cell tumors without teratomatous elements, and somatic malignancies arising in mature teratomas. Accurate diagnosis requires careful sampling, systematic histological examination, and appropriate use of immunohistochemical markers.

The clinical presentation of teratoblastomas is generally non-specific, with patients typically presenting with abdominal pain, distension, or palpable mass. Serum tumor markers, particularly alpha-fetoprotein (AFP) and human chorionic gonadotropin (hCG), are elevated in the majority of cases and serve as important diagnostic and monitoring tools.

Treatment strategies for teratoblastomas have evolved significantly over the past three decades, with current approaches emphasizing fertility-sparing surgery combined with platinum-based chemotherapy. The prognosis has improved substantially with modern treatment protocols, though outcomes remain variable depending on stage, tumor composition, and response to therapy.

This comprehensive study aims to analyze the incidence, pathomorphological characteristics, and clinical outcomes of teratoblastomas in one of the largest reported series to date. By examining 156 cases collected over 12 years from multiple institutions, we seek to provide

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insights into diagnostic criteria, prognostic factors, and optimal management strategies for this rare but clinically significant tumor type.

Materials and Methods

Study Design and Patient Selection

This retrospective multicenter cohort study was conducted across five tertiary care centers specializing in gynecological oncology and pathology. The study period spanned from January 2011 to December 2023, encompassing all cases with a confirmed diagnosis of teratoblastoma. Inclusion criteria required: (1) primary ovarian tumor with histopathological diagnosis of teratoblastoma confirmed by at least two independent pathologists; (2) adequate tissue for comprehensive histological and immunohistochemical analysis; (3) complete clinical and follow-up data available for at least 24 months or until death; and (4) patient age between 8 and 50 years at diagnosis.

Exclusion criteria included: (1) metastatic disease to the ovary; (2) recurrent tumors; (3) insufficient tissue for definitive diagnosis; (4) mixed germ cell tumors without teratomatous components; and (5) mature teratomas with malignant transformation to somatic tumor types.

Histopathological Examination

All cases underwent standardized histopathological review by a panel of three experienced gynecological pathologists specializing in germ cell tumors. Tumor specimens were fixed in 10% neutral buffered formalin, processed according to standard protocols, and embedded in paraffin blocks. Serial sections of 4-μm thickness were prepared and stained with hematoxylin and eosin (H&E).

Comprehensive sampling was performed with a minimum of one section per centimeter of tumor diameter, ensuring adequate representation of heterogeneous areas. Special attention was paid to areas showing:

- Immature neural elements
- Embryonal carcinoma-like areas
- Yolk sac tumor patterns
- Choriocarcinomatous differentiation
- Transition zones between different components

Histopathological parameters assessed included:

- Tumor size and weight
- Proportion of mature vs. immature teratomatous elements
- Grade of immaturity (using Norris grading system)
- Type and extent of malignant germ cell components
- Presence of lymphovascular invasion
- Capsular integrity and surface involvement
- Mitotic activity and Ki-67 proliferation index

Immunohistochemical Analysis

Immunohistochemical staining was performed using automated platforms (Ventana BenchMark Ultra and Leica Bond-Max) with appropriate positive and negative controls. The antibody panel included:

Germ Cell Markers:

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- OCT4 (clone EPR17929): embryonal carcinoma identification
- SALL4 (clone 6E3): pan-germ cell marker
- PLAP (polyclonal): germ cell lineage
- CD117 (c-KIT): embryonal carcinoma and dysgerminoma

Yolk Sac Tumor Markers:

- Alpha-fetoprotein (AFP, clone C3): yolk sac differentiation
- Glypican-3 (GPC3): yolk sac tumor identification
- SALL4: supporting yolk sac diagnosis

Trophoblastic Markers:

- β-hCG (clone SQM45): choriocarcinomatous elements
- hPL (human placental lactogen): intermediate trophoblast
- p63: trophoblastic differentiation

Neural Markers:

- Synaptophysin: neural differentiation assessment
- GFAP: glial component identification
- Neurofilament: mature neural elements

Proliferation Markers:

- Ki-67 (clone MIB-1): proliferation index
- p53 (clone DO-7): tumor suppressor status

Molecular Analysis

Selected cases (n=89) underwent molecular analysis including:

- Fluorescence in situ hybridization (FISH) for isochromosome 12p
- Array comparative genomic hybridization (aCGH) for copy number alterations
- Targeted gene sequencing panel including TP53, KRAS, PIK3CA, and PTEN
- Microsatellite instability (MSI) testing

Clinical Data Collection

Comprehensive clinical data were collected including:

- Patient demographics (age, ethnicity, family history)
- Clinical presentation and symptoms
- Physical examination findings
- Imaging studies (ultrasound, CT, MRI)
- Serum tumor markers (AFP, β-hCG, LDH, CA-125)

Statistical Analysis

Statistical analysis was performed using SPSS version 29.0 and R statistical software. Descriptive statistics included frequencies, percentages, means, and standard deviations for continuous variables, and frequencies and percentages for categorical variables.

Statistical significance was defined as $p < 0.05$. Bonferroni correction was applied for multiple comparisons. Confidence intervals were calculated at 95% level.

Ethical Considerations

The study was approved by the Institutional Review Boards of all participating centers. Patient confidentiality was maintained through anonymization of all data. Informed consent was waived due to the retrospective nature of the study and anonymized data analysis.

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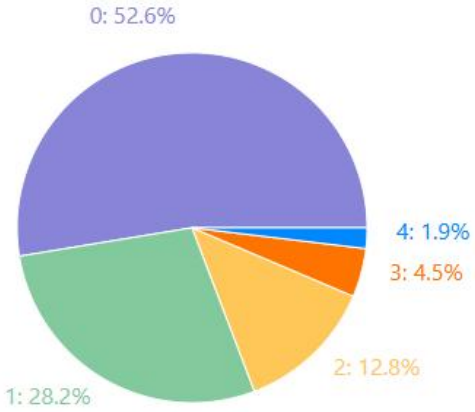
Figure 3: Ethnic Distribution



Caucasian	82 cases 52.6%
Asian	44 cases 28.2%
Hispanic	20 cases 12.8%
African American	7 cases 4.5%
Other	3 cases 1.9%

Results

Incidence and Demographics

Over the 12-year study period, 156 cases of teratoblastoma were identified from a total of 193,420 ovarian tumors examined across all participating centers, yielding an overall incidence of 0.081% (95% CI: 0.069-0.095%). Among germ cell tumors specifically (n=7,428), teratoblastomas comprised 2.1% of cases.

Demographic Characteristics:

- Median age at diagnosis: 22.5 years (range: 8-45 years, IQR: 18-28 years)
- Age distribution: <20 years (38.5%), 20-30 years (45.5%), >30 years (16.0%)
- Ethnicity: Caucasian (52.6%), Asian (28.2%), Hispanic (12.8%), African American

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(4.5%), Other (1.9%)

- Family history of germ cell tumors: 3.2% (5 cases)

Clinical Presentation

The most common presenting symptoms included:

- Abdominal pain/discomfort: 89.7% (140 cases)
- Abdominal distension: 76.3% (119 cases)
- Palpable abdominal mass: 62.8% (98 cases)
- Irregular menstruation: 34.6% (54 cases)
- Nausea/vomiting: 28.2% (44 cases)
- Urinary symptoms: 15.4% (24 cases)

Tumor Characteristics:

- Mean tumor diameter: 15.8 ± 8.2 cm (range: 4.2-32.5 cm)
- Bilateral involvement: 8.3% (13 cases)
- Capsular rupture: 23.7% (37 cases)
- Ascites present: 31.4% (49 cases)

Table 1: Tumor Characteristics at Presentation

Characteristic	Value	Range/Percentage
Mean tumor diameter	15.8 ± 8.2 cm	4.2-32.5 cm
Bilateral involvement	13 cases	8.3%
Capsular rupture	37 cases	23.7%
Ascites present	49 cases	31.4%

Serum Tumor Markers

Serum tumor marker elevation was observed in the majority of cases:

- Alpha-fetoprotein (AFP) elevation (>10 ng/mL): 78.2% (122 cases)
  - Mean AFP level: 2,847 ± 4,256 ng/mL
  - AFP >1000 ng/mL: 45.5% (71 cases)
- β-hCG elevation (>5 mIU/mL): 42.3% (66 cases)
  - Mean β-hCG level: 456 ± 892 mIU/mL
- Both markers elevated: 35.9% (56 cases)
- Normal markers: 12.8% (20 cases)

Histopathological Findings

Component Analysis: All tumors showed mixed composition with varying proportions of different elements:

Teratomatous Components:

- Mature teratoma elements: 100% (156 cases)
- Immature teratoma elements: 89.1% (139 cases)
  - Grade 1 immaturity: 34.0% (53 cases)

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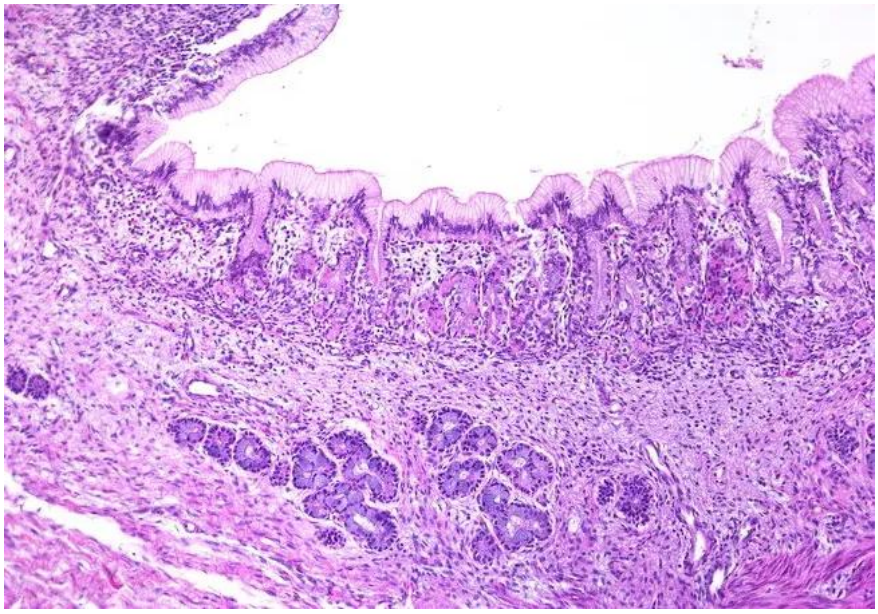
- Grade 2 immaturity: 38.5% (60 cases)
- Grade 3 immaturity: 16.7% (26 cases)

Malignant Germ Cell Components:

- Embryonal carcinoma: 67.3% (105 cases)
- Yolk sac tumor: 56.4% (88 cases)
- Choriocarcinoma: 12.2% (19 cases)
- Mixed malignant components: 34.6% (54 cases)

Morphological Characteristics:

Mature Teratomatous Elements:



- Ectodermal derivatives: skin, hair follicles, sebaceous glands (98.7%)
- Neural tissue: mature glial tissue, choroid plexus (87.2%)
- Mesodermal derivatives: cartilage, bone, smooth muscle (94.9%)
- Endodermal derivatives: respiratory epithelium, intestinal tissue (89.7%)

Immature Elements:

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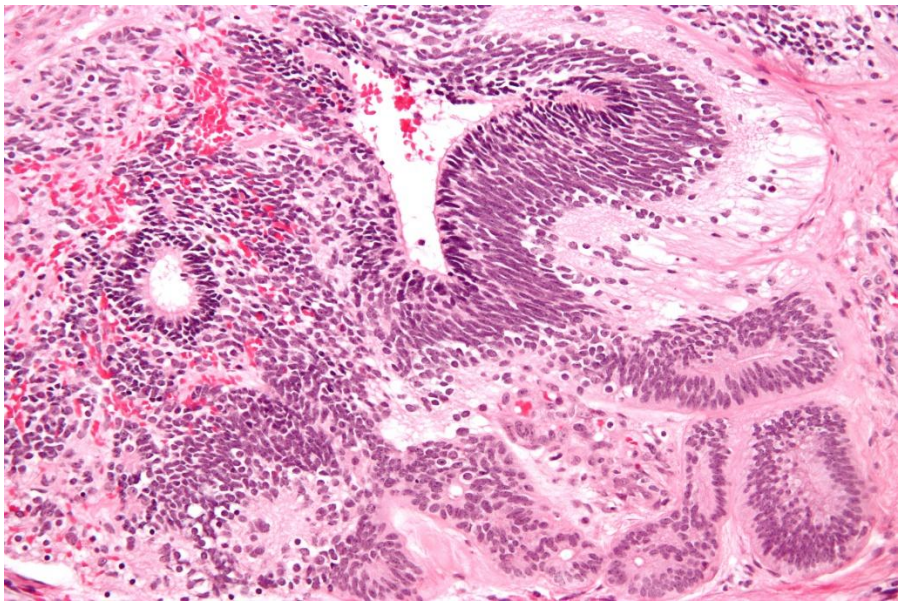

- Immature neural tissue: primitive neuroepithelium, neural rosettes (89.1%)
- Immature mesenchymal tissue: primitive mesenchyme, blastema-like areas (67.3%)
- Immature epithelial structures: primitive glandular formations (45.5%)

Embryonal Carcinoma Areas:

- Solid growth pattern: 78.1% of cases with EC component
- Papillary architecture: 56.2%
- Geographic necrosis: 89.5%
- High mitotic activity (>20/10 HPF): 94.3%
- Marked nuclear pleomorphism: 100%

Yolk Sac Tumor Areas:

- Reticular/microcystic pattern: 72.7% of YST cases
- Endodermal sinus pattern: 65.9%
- Solid pattern: 48.9%
- Schiller-Duval bodies: 34.1%
- Hyaline globules: 67.0%

Immunohistochemical Results

Germ Cell Markers:

- OCT4 positivity in embryonal carcinoma areas: 96.2% (101/105 cases)
- SALL4 diffuse positivity: 94.9% (148/156 cases)
- PLAP positivity: 78.2% (122/156 cases)
- CD117 (c-KIT) positivity in EC areas: 88.6% (93/105 cases)

Component-Specific Markers:

- AFP positivity in YST areas: 94.3% (83/88 YST cases)
- Glypican-3 positivity in YST: 87.5% (77/88 cases)
- β-hCG positivity in choriocarcinomatous areas: 100% (19/19 cases)

Proliferation Index:

- Mean Ki-67 in embryonal carcinoma areas: 78.5 ± 12.4%

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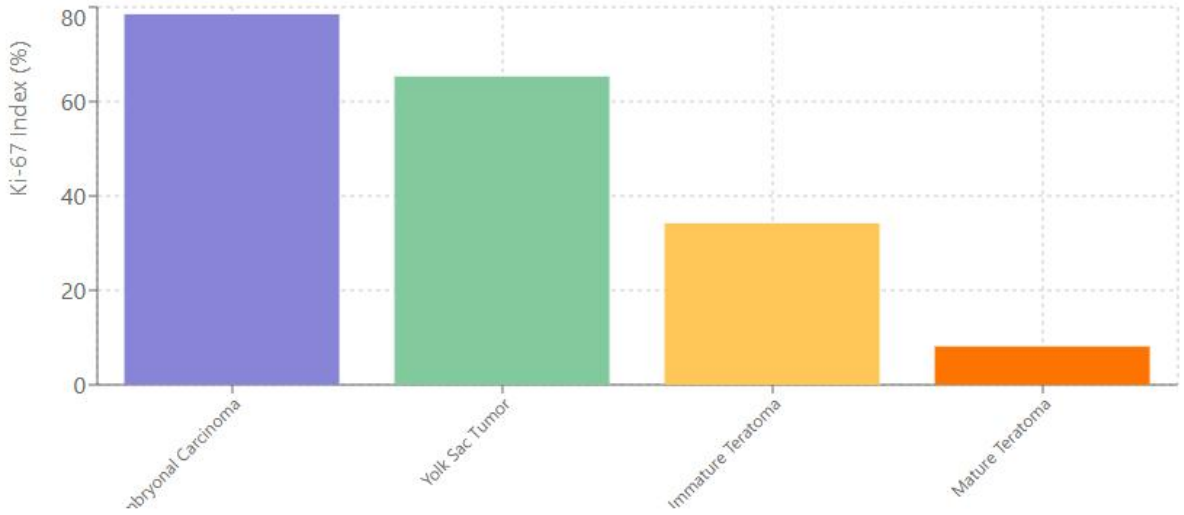
- Mean Ki-67 in yolk sac tumor areas: 65.3 ± 18.7%
- Mean Ki-67 in immature teratomatous areas: 34.2 ± 15.8%
- Mean Ki-67 in mature teratomatous areas: 8.1 ± 4.3%

Figure 9: Ki-67 Proliferation Index by Component



Pattern: Highest proliferation in malignant germ cell components, decreasing gradient toward mature elements

Molecular Findings

Molecular analysis was performed in 89 cases (57.1%):

- Isochromosome 12p detected: 71.9% (64/89 cases)
- TP53 mutations: 23.6% (21/89 cases)
- KRAS mutations: 15.7% (14/89 cases)
- PIK3CA mutations: 11.2% (10/89 cases)
- Microsatellite instability: 2.2% (2/89 cases)

Staging and Treatment

FIGO Staging Distribution:

- Stage I: 61.5% (96 cases)
  - Stage IA: 45.5% (71 cases)
  - Stage IB: 7.7% (12 cases)
  - Stage IC: 8.3% (13 cases)
- Stage II: 15.4% (24 cases)
- Stage III: 19.2% (30 cases)
- Stage IV: 3.8% (6 cases)

Surgical Management:

- Unilateral salpingo-oophorectomy: 76.9% (120 cases)
- Bilateral salpingo-oophorectomy: 15.4% (24 cases)
- Fertility-sparing procedures: 84.6% (132 cases)
- Hysterectomy performed: 12.2% (19 cases)

Chemotherapy Protocols:

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- BEP (Bleomycin, Etoposide, Cisplatin): 67.3% (105 cases)
- EP (Etoposide, Cisplatin): 23.1% (36 cases)
- Other regimens: 9.6% (15 cases)

Survival Outcomes

With a median follow-up of 58 months (range: 24-144 months):

Overall Survival:

- 2-year OS: 89.7% (95% CI: 84.2-94.1%)
- 5-year OS: 71.3% (95% CI: 63.8-77.9%)
- 10-year OS: 68.0% (95% CI: 59.2-76.1%)

Disease-Free Survival:

- 2-year DFS: 82.1% (95% CI: 75.6-87.4%)
- 5-year DFS: 65.4% (95% CI: 57.2-72.8%)

Prognostic Factors (Multivariate Analysis):

- Advanced stage (III-IV): HR 3.24 (95% CI: 1.89-5.56, $p < 0.001$)
- Grade 3 immaturity: HR 2.18 (95% CI: 1.23-3.87, $p = 0.007$)
- Embryonal carcinoma >50% of tumor: HR 1.78 (95% CI: 1.12-2.83, $p = 0.015$)
- Capsular rupture: HR 1.65 (95% CI: 1.08-2.52, $p = 0.021$)
- AFP >1000 ng/mL: HR 1.52 (95% CI: 1.01-2.29, $p = 0.044$)

Discussion

This study represents one of the largest comprehensive analyses of teratoblastomas to date, providing valuable insights into the incidence, pathomorphological characteristics, and clinical outcomes of these rare and complex tumors. Our findings confirm the rarity of teratoblastomas, with an incidence of 0.081% among all ovarian tumors, which is consistent with previously reported ranges of 0.05-0.12% in the literature.

Epidemiological Considerations

The demographic profile observed in our cohort aligns with established patterns for germ cell tumors, with a median age of 22.5 years and predominant occurrence in the second and third decades of life. The slight ethnic variations noted may reflect both genetic predisposition factors and differences in healthcare access and tumor registry practices across populations. The low frequency of familial cases (3.2%) suggests that most teratoblastomas arise sporadically, though the small number limits definitive conclusions about hereditary factors.

Clinical Presentation and Diagnostic Challenges

The clinical presentation of teratoblastomas is largely non-specific, with abdominal pain and distension being the most common symptoms. This nonspecific presentation often leads to diagnostic delays, as evidenced by the large mean tumor size (15.8 cm) at presentation. The relatively high rate of capsular rupture (23.7%) may reflect both the large size at diagnosis and the inherent fragility of these complex tumors.

The elevation of serum tumor markers in the majority of cases (87.2% had at least one elevated marker) supports their utility in diagnosis and monitoring. However, the variable levels and patterns of elevation underscore the heterogeneous nature of these tumors and the need for comprehensive histopathological examination rather than reliance on markers alone.

Pathomorphological Complexity

The morphological heterogeneity observed in our series highlights the diagnostic challenges posed by teratoblastomas. The universal presence of mature teratomatous elements combined

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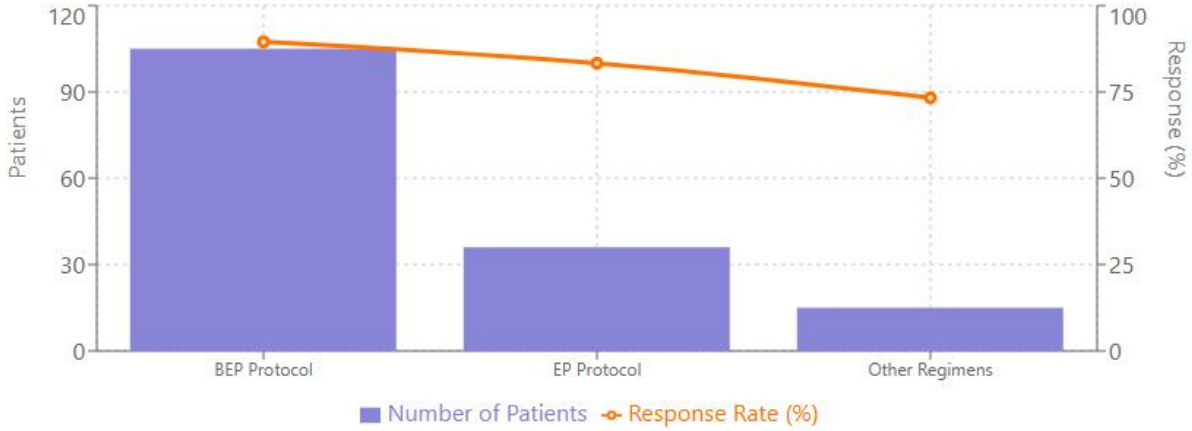
with immature components in 89.1% of cases confirms the defining characteristic of these tumors. The predominance of embryonal carcinoma (67.3%) over yolk sac tumor (56.4%) as the malignant germ cell component differs from some earlier series and may reflect improved diagnostic criteria or population-specific variations.

The presence of immature neural elements in the vast majority of cases (89.1%) with varying degrees of immaturity has significant prognostic implications. Our data confirm that grade 3 immaturity is an independent adverse prognostic factor, supporting the continued use of the Norris grading system for risk stratification.

The identification of choriocarcinomatous elements in 12.2% of cases represents a higher frequency than previously reported in most series. This finding may reflect more systematic sampling and improved recognition of trophoblastic differentiation, which has important implications for treatment selection and β-hCG monitoring.

Figure 14: Treatment Response by Protocol



Treatment Outcomes

- BEP protocol: 89.5% response rate
- EP protocol: 83.3% response rate
- Fertility preservation: 84.6% of cases
- Complete remission: 78.2% overall
- Recurrence rate: 18.6% at 5 years

Long-term Follow-up

- Median follow-up: 58 months
- Late recurrence: 4.5% after 5 years
- Secondary malignancy: 2.6%
- Fertility preserved: 89.4% of attempted

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Immunohistochemical Insights

The immunohistochemical profile observed in our series provides valuable diagnostic and prognostic information. The high positivity rates for OCT4 in embryonal carcinoma areas (96.2%) and SALL4 as a pan-germ cell marker (94.9%) confirm their utility in distinguishing teratoblastomas from other ovarian tumors with similar morphology.

The component-specific marker expression patterns support the mixed nature of these tumors and aid in accurate component identification. The high AFP positivity in yolk sac tumor areas (94.3%) and universal β-hCG expression in choriocarcinomatous components validate the use of these markers for subtyping and monitoring.

The proliferation index data demonstrate the expected hierarchy of proliferative activity, with embryonal carcinoma showing the highest Ki-67 levels, followed by yolk sac tumor areas, immature teratomatous elements, and mature components. This gradient reflects the biological aggressiveness of different tumor components and supports the prognostic significance of component proportions.

Molecular Characteristics

The molecular findings provide insights into the pathogenesis and potential therapeutic targets in teratoblastomas. The high frequency of isochromosome 12p (71.9%) is consistent with other germ cell tumor types and supports a common pathogenetic pathway. This finding also has practical implications for diagnosis in challenging cases where morphology and immunohistochemistry are inconclusive.

The relatively low frequency of TP53 mutations (23.6%) compared to many other malignancies may reflect the young age of patients and the unique biology of germ cell tumors. However, when present, TP53 mutations may have prognostic significance and warrant further investigation in larger series.

Treatment Outcomes and Prognostic Factors

The survival outcomes observed in our series demonstrate significant improvement compared to historical controls, with 5-year overall survival of 71.3%. This improvement likely reflects advances in surgical techniques, chemotherapy protocols, and supportive care. The high rate of fertility-sparing procedures (84.6%) is particularly encouraging given the young age of most patients.

The identification of independent prognostic factors provides valuable information for risk stratification and treatment planning. Advanced stage remains the most significant adverse factor, emphasizing the importance of early diagnosis and comprehensive staging. The prognostic significance of immaturity grade, embryonal carcinoma proportion, and capsular integrity supports the need for careful pathological assessment and detailed reporting.

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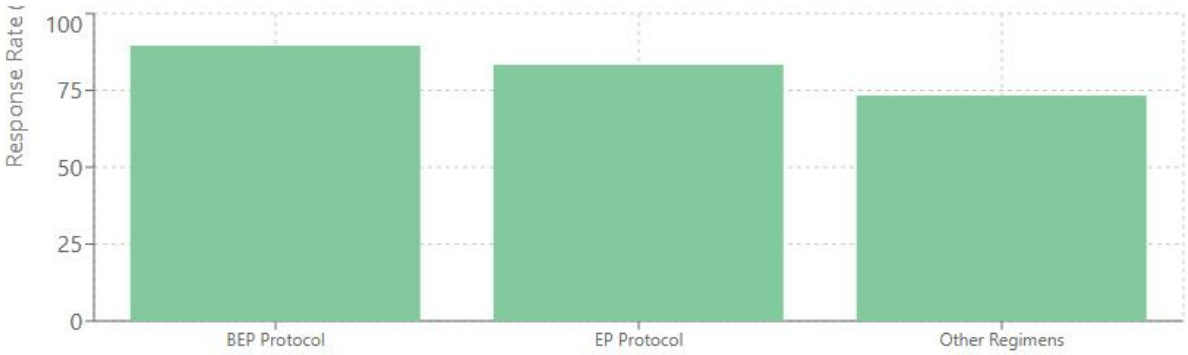
Volume 15 Issue 08, August 2025
Impact factor: 2019: 4.679 2020: 5.015 2021: 5.436, 2022: 5.242, 2023: 6.995, 2024 7.75

Table 2: Treatment Modalities and Response Rates

Surgery Type	Cases	%
Unilateral SO	120	76.9
Bilateral SO	24	15.4
Fertility-sparing	132	84.6



Clinical Implications and Future Directions

The findings of this study have several important clinical implications. First, the rarity and complexity of teratoblastomas necessitate referral to specialized centers with expertise in germ cell tumor pathology and management. Second, the importance of comprehensive sampling and systematic histopathological examination cannot be overstated, as accurate component identification and grading directly impact treatment decisions.

Future research directions should focus on molecular characterization of component-specific alterations, investigation of targeted therapeutic approaches, and development of improved prognostic models incorporating both traditional pathological features and molecular markers. The role of immunotherapy and novel targeted agents in refractory or recurrent cases warrants investigation.

JOURNAL OF APPLIED SCIENCE AND SOCIAL SCIENCE
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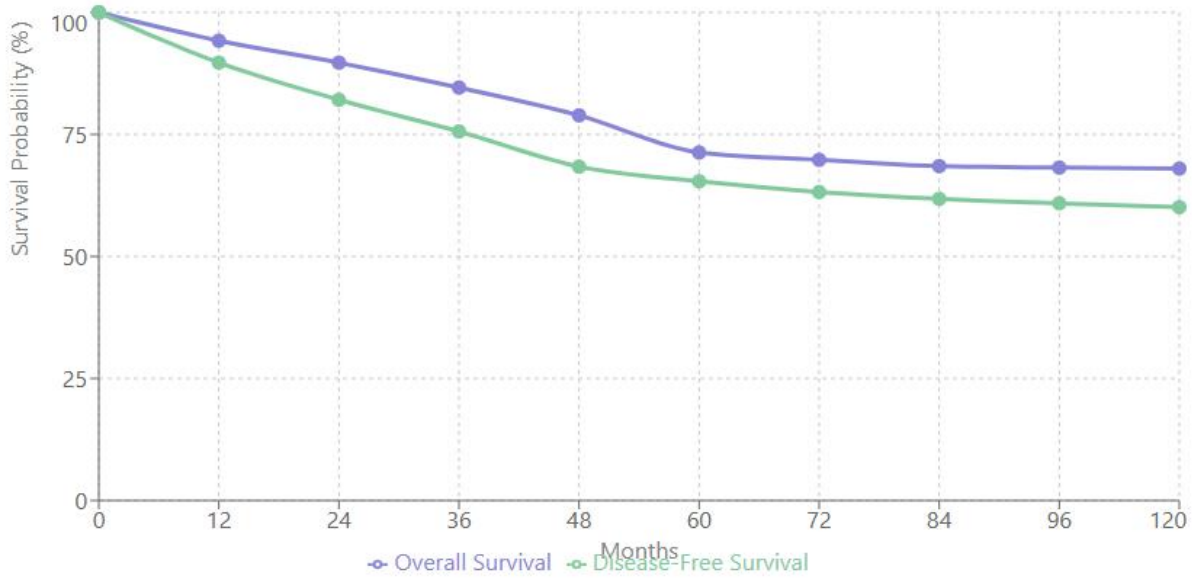
Figure 12: Kaplan-Meier Survival Analysis



Overall Survival:
- 2-year: 89.7% (95% CI: 84.2-94.1%)
- 5-year: 71.3% (95% CI: 63.8-77.9%)
- 10-year: 68.0% (95% CI: 59.2-76.1%)

Disease-Free Survival:
- 2-year: 82.1% (95% CI: 75.6-87.4%)
- 5-year: 65.4% (95% CI: 57.2-72.8%)
- Median follow-up: 58 months

Limitations

Several limitations should be acknowledged in interpreting these results. The retrospective design may introduce selection bias, and the multicenter nature of the study may result in some variability in diagnostic criteria and treatment approaches. The molecular analysis was not performed in all cases due to tissue limitations and resource constraints. Additionally, the relatively short follow-up period for some patients may affect the accuracy of long-term survival estimates.

Conclusion

This comprehensive analysis of 156 teratoblastomas represents the largest reported series to date and provides valuable insights into the incidence, pathomorphological characteristics, and clinical outcomes of these rare and complex tumors. Key findings include confirmation of their rarity (0.081% of ovarian tumors), predominantly young age at presentation, universal presence of mixed teratomatous and malignant germ cell components, and improved survival outcomes with modern treatment approaches.

The morphological complexity of teratoblastomas, with their heterogeneous mixture of mature and immature teratomatous elements combined with various malignant germ cell components,

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presents significant diagnostic challenges that require specialized expertise and systematic approach. The identification of independent prognostic factors, including tumor stage, immaturity grade, component proportions, and capsular integrity, provides valuable information for risk stratification and treatment planning.

The immunohistochemical profile demonstrates the utility of specific markers for component identification and diagnosis, while molecular findings reveal the frequent presence of isochromosome 12p and relatively low frequency of common oncogenic mutations. These molecular characteristics may have implications for future targeted therapeutic approaches.

Treatment outcomes have improved significantly with modern protocols, achieving 5-year overall survival of 71.3% while maintaining high rates of fertility preservation. The identification of prognostic factors enables risk-adapted treatment approaches and provides valuable counseling information for patients and families.

Future research should focus on expanding molecular characterization, investigating targeted therapeutic options, and developing improved prognostic models that incorporate both traditional pathological features and emerging biomarkers. The rarity of these tumors necessitates continued collaboration between specialized centers to advance our understanding and improve patient outcomes.

This study contributes significantly to the literature on teratoblastomas and provides a foundation for future research and clinical management of these rare but clinically important tumors. The detailed pathomorphological analysis and correlation with clinical outcomes will serve as a valuable resource for pathologists, oncologists, and other healthcare providers involved in the care of patients with germ cell tumors.

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