

## Teratoma in Children: Three cases experience in Sanglah Hospital, Bali, Indonesia

Ni Putu Indah Kusumadewi Riandra <sup>1,\*</sup>, Ketut Ariawati <sup>1</sup>, Aank Agung Ngurah Ketut Putra Widnyana <sup>1</sup>, Luh Putu Iin Indrayani Maker <sup>2</sup> and I Gusti Ayu Ari Kusumawati <sup>3</sup>

<sup>1</sup> Department of Child Health, Faculty of Medicine, Udayana University/Sanglah General Hospital, Denpasar, Bali, Indonesia.

<sup>2</sup> Department of Pathology-Anatomy, Faculty of Medicine, Udayana University/Sanglah General Hospital, Denpasar, Bali, Indonesia.

<sup>3</sup> Department of Pathology-Anatomy, Klungkung Hospital, Klungkung, Indonesia.

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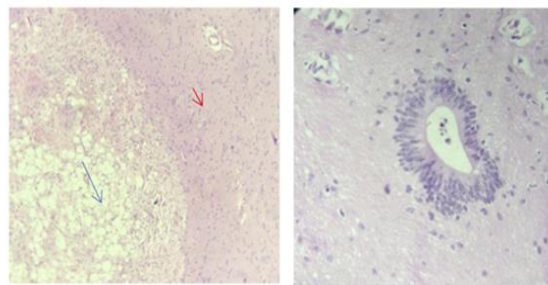
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### Abstract

Teratomas are the most common germ cell tumor, and further classified into mature or immature. Immature teratoma comprise less than one percent of all teratomas and with the peak incidence at birth until four years. They were diagnosed by history taking, physical examination, laboratory, imaging, and pathological anatomy as a gold standard. This report presents our experience of diagnosed, giving treatment with or without surgery and chemotherapy in three patients with teratoma. We report three cases of teratoma, at age six months, eight months and four years old with site of cases are retroperitoneal immature teratoma, cervical teratoma and ovarian immature teratoma. History taking of these patients, they have same symptom such as enlargement of the mass. Two cases were noticed after birth and progressively getting bigger until six and eight months old. One case was noticed when the patient had abdominal pain and was suspected with appendicitis at first. The computed tomography (CT) scan of these cases showed a mass as a part of teratoma and confirmed with pathological anatomy. Two cases were immature, and one case was mature teratoma. Two patients undergone surgery resection and continue with chemotherapy (cisplatin, etoposide, and bleomycin) for 10-14 weeks showed a good result until now and showed no residual mass anymore form CT scan, but one patient did not undergo surgery and chemotherapy yet. Early diagnosis of teratomas is leading us to a definitive therapy and showed a good result.

**Keywords:** *immature teratoma; diagnosis; treatment; children*

### Graphical Abstract



The different of component mature teratoma; glial cell and mature fat (a) and immature teratoma component such as neuroectodermal formed a rosette structure (b),

\* Corresponding author: Ni Putu Indah Kusumadewi Riandra  
Department of Child Health, Faculty of Medicine Udayana University/Sanglah Hospital Jalan Diponegoro, Denpasar, Bali, Indonesia.

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## 1. Introduction

Teratomas are the most common germ cell tumor, whether mature or immature. A mature teratoma is a benign tumor, whereas the immature type, although benign, has a more aggressive course, with a propensity to recurrence [1]. The designation teratoma refers to a neoplasm that differentiates toward somatic-type cell populations (typically including cell populations that would normally derive from ectoderm, endoderm, and mesoderm) that can be typical of either adult or embryonic development. The component tissues in a teratoma range from immature to well differentiated and are foreign to the anatomic site in which they are found. Teratomas are divided into four categories: mature (cystic or solid, benign), immature (malignant), malignant due to a component of another somatic malignant neoplasm, and monoderm or highly specialized [2].

Immature teratomas are also called malignant teratoma, teratoblastoma, or embryonal teratoma may arise from any organ but the majority are found in the ovary, testis, sacrococcygeal region and mediastinum [3]. They comprise less than one percent of ovarian teratomas and are most common in the first two decades of life. They comprise 35.6 percent of all malignant ovarian germ cell tumors (OGCT). These neoplasms are typically composed of tissue from the three germ cell layers: ectoderm, mesoderm, and endoderm, arranged in a haphazard manner. Histologically, there are varying amounts of immature tissue, most frequently with neural differentiation, although immature stromal elements can also be present. Immature teratomas are the only OGCTs that are histologically graded. The grade of differentiation (ranging from I [well differentiated] to III [poorly differentiated]) is based upon the proportion of tissue in histologic sections containing immature neural elements [1, 4]. Grade is an important indicator of the risk for extra ovarian spread. In some cases, alpha fetoprotein (AFP) or lactate dehydrogenase (LDH) may be elevated. A rare condition associated with either mature or immature teratomas is anti-N-methyl-D-aspartate (NMDA) receptor encephalitis [4].

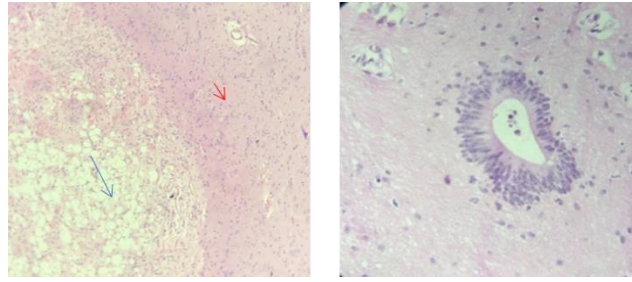
Immature teratoma are diagnosed by history taking, physical examination, laboratories, histology, and imaging evaluation. Early diagnosed of teratomas are leading us to a definitive therapy such as surgery for resection and chemotherapy. In this paper, we present the experience of Department of Child Health and Pathological Anatomy in diagnose and managing some cases of teratoma. The objective of this case series is to describe the clinical presentation, histology, therapy, and outcome of different anatomy site of teratomas.

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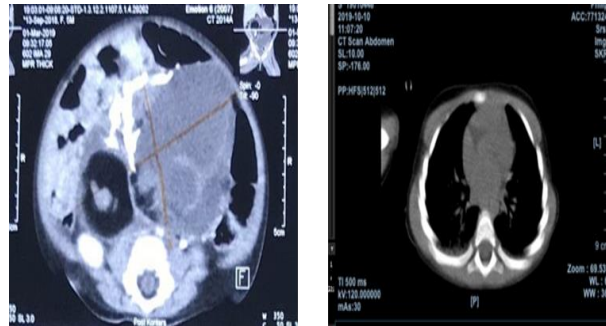
## 2. Case Report

### 2.1. First Case

A 6-month-old girl was hospitalized due to abdominal mass since birth and getting bigger by the time. The mass was identified in the abdomen. Abdominal distension, abdominal pain, diarrhea and fever were denied. No evident abnormalities or significant weight loss were observed. The result of physical examination revealed the presence of abdominal distention and clear abdominal veins. No evident dilation or bowel obstruction was identified. A large mass (11x7x7cm) was palpable below the xiphoid in the epigastrium. The mass, which ranged from the xiphoid to the umbilical region, was friable and had smooth surface, clear boundaries, without any tenderness. The complete blood count (CBC) examination was within normal limit and Alpha Fetoprotein (AFP) was 6.91 IU/mL (normal limit was below than 5.8 IU/mL). Upper abdominal computed tomography (CT) revealed a large, solid mass in the retroperitoneum. The internal diameter of the mass was indicated to measure 11 x 8 x 6.9 cm, multilobulated, with soft tissue density component, cystic and irregular calcification, fat and dentes form. The disease was likely to be diagnosed as a teratoma based on the imaging data. Retroperitoneal tumor resection was subsequently performed. During resection, the tumor was found originate from the retroperitoneal space, the measure was 14 x 12,8 cm. The mass was close with aorta abdominal, inferior cava vein, and superior right kidney. The mass was contained serous, fat look mass and bone look mass. The pathologically examined tumor tissue, the resection surface was white and friable, with a portion that appeared similar to rotten meat, multiple lobes and contained liquids and mucous. A severe quantity of immature neuron and mesenchymal components were evident in the microscopic examination of the tumor, with large amount of immature neuroepithelial tissue occupying > 3 low power field (40x), which was diagnosed by pathology as grade III immature teratoma (Figure 1A and B). After resection, we performed a CT Scan (Figure 2A and B) and revealed a large, solid mass in the middle intraperitoneal. The internal diameter of the mass was 7.44 x 4.35 x 5.12 cm without cystic or calcification. Following by contrast-enhanced CT scan the solid region of the tumor demonstrated enhancement and was shifted upon compression near the intestine and made a partial obstruction in the intestine. The disease was likely to be diagnosed as a middle retroperitoneal malignant tumor based on the imaging data. Patient subsequently receiving chemotherapy for 10 weeks. The chemotherapy consisted of Bleomycin, Etoposide and Cisplatin. After chemotherapy, we performed CT Scan evaluation and revealed there are a thickened of small intestinal systemic wall due to inflammation process and there is no clear sign of abdominal mass anymore (Figure 2B).



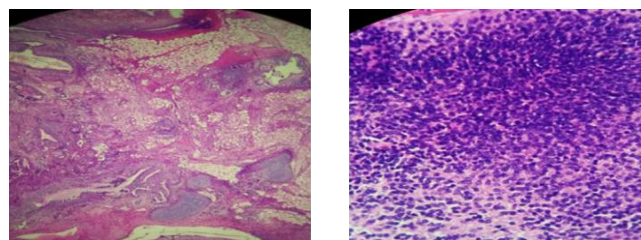
**Figure 1** (a) component mature; glial cell and mature fat. 1(b): Neuroectodermal formed a rosette structure (H7E, 400x)



**Figure 2** (a) Computed Tomography of abdomen with contrast showed abdominal mass (11x8x6.9 cm) lobulated, fluid density, fat, calcification (+), and soft tissue density. Kidney was pushed to the posterior due to the abdominal mass. 2(b): There is no sign of abdominal mass after surgery and chemotherapy.

## 2.2. Second Case

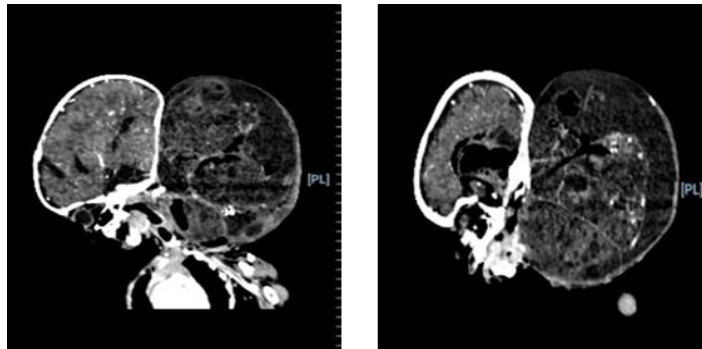
A 4-year-old girl was hospitalized due to abdominal mass and pain since 2 days before admission. At first, the parents did not notice the mass in the abdomen. However, 2 days prior to admission, Patient complained abdominal pain and distended. Physical examination revealed distended abdomen, with pain in all region of abdomen, mass was difficult to evaluation due to extremely pain. At first, the Surgeon thought that was an acute abdomen caused by appendicitis, so they did a laparotomy and found appendicitis and one mass in the tuba and ovarium mass with the size was approximately 11 x 8 x 4 cm. The mass was contained cartilage, fat, and immature mesenchyme. The CBC examination was within normal limit and AFP was 1.37 IU/mL (normal was below than 5.8 IU/mL). The surgeon done the resection and did Pathology Anatomy examination. Pathological examination of tumor tissue sections also revealed the involvement of immature neuroectodermal, tubules and rosette, that occupying 1-3 power fields (40x) in any slide, confirming the diagnosis of a grade II immature teratoma (Figure 3A and B). Patient is doing a chemotherapy for 18 weeks. The chemotherapy was contained Cisplatin, Etoposide and Bleomycin. We performed CT Scan after chemotherapy and revealed there is no sign of abdominal mass (residual mass), a picture of atypical lymphadenopathy inguinal bilateral and there is no sign of liver metastases.



**Figure 3** (a) Ovarium tissue consists of cartilage, fat, gastrointestinal epitel, keratin glial cell, choroid, ganglion, and glandular. 3(b): immature neuroectodermal and pseudorosette was performed by overlapping hyperchromatic cell (H&E, 400x)

### 2.3. Third Case

Female, 8th months old was hospitalized due to enlargement of coli mass since birth and getting bigger by the time until today. The mass was identified in the neck and getting bigger to the head. The children demonstrated enlargement of neck mass, feeding difficulties but no pain. The patient was slept well and still had a good appetite. No evident abnormalities or significant weight loss were observed. The result of physical examination revealed the presence of cervical mass. A large mass (30x20 cm) on the left coli. The mass, which ranged from the left coli until left ear. The mass was friable and possessed a smooth surface, clear boundaries, without tenderness. The complete blood count (CBC) examination was showed hypochromic microcyte anemia and thrombocytosis. Alpha Fetoprotein (AFP) was 7184 IU/mL (normal was below than 5.8 IU/mL). Head and coli computed tomography (CT) (Figure 5) revealed left cervical teratoma (11.7 x 16.7 x 16 cm at the cervical and 5 x 5.6 x 6.3 cm at the intracranial lesion) with enlargement to left temporal lobes and destructions on left mastoid, pressing the left communis carotid artery to medial, calvaria to right lateral, and left clavicula bones to inferior. In the intracranial lesion had pressing to left lateral ventricle and had midline shift to the right (0.6 cm). The disease was likely to be diagnosed as a teratoma based on the imaging data. The cervical resection could not be done due to location and massive bleeding risk were concerned. Pediatric surgeon was done a biopsy. During biopsy, tissue was taken just + 0.5-0.7 cm due to massive bleeding. The pathologically examined tumor tissue, the resection surface was white and friable, with a portion that appeared similar to fibrous, fat, vessels and lymphoid and can be diagnosed as teratoma but they needed more sample to examine and grading this teratoma. From the history taking, blood examination and imaging, patient was diagnosed with cervical teratoma, and patient was planned to do a chemotherapy for 19 weeks. The chemotherapy contained Bleomycin, Etoposide and Cisplatin. After chemotherapy, we need to performed CT Scan evaluation.



**Figure 5** Computed Tomography of head and coli with contrast showed cervical mass (11.7 x 16.7 x 16 cm at left coli and 5 x 5.6 x 6.3 cm at intracranial lesion) lobulated, fluid density, fat, calcification (+), and soft tissue density. Destruction on left mastoid, pressing the left communis carotid artery to medial, calvaria to right lateral, and left clavicula bones to inferior. In the intracranial lesion had pressing to left lateral ventricle and had midline shift to the right (0.6 cm).

### 3. Discussion

Pediatric germ cell tumors are rare disease and only 1-3% of total childhood tumor. Remarkably diverse group with significant variability in age and site of presentation, clinical behavior, and histology. They share a common origin from progenitor germ cells. The three major types include teratoma, yolk sac tumor and seminoma or dysgerminoma. Majority of pediatric germ cell tumors are benign, but 20% of pediatric GCTs are malignant and only 3% of all pediatric cancers. Risk factor for GCTs are GCTs lack familial distribution, thought to arise from sporadic genetic mutations, chromosomal mutations, and maternal exposure to various chemicals and solvents may increase of GCT [5]. Diagnostic approach in teratoma is by history of mass enlargement and pain on the mass, laboratories finding with level of alpha fetoprotein (AFP), imaging with CT Scan revealed a mass contained teratomas, and pathology anatomy from tumor resection showed immature teratoma. Early diagnosed of teratomas are leading us to a definitive therapy such as surgery for resection and chemotherapy.

Teratomas are one of the most common germ cell tumors accounting for approximately 25 percent of all germ cell tumors with a yearly incidence of 1 in 40,000 live births. Teratomas are embryonic tumors that are derived from two to three germinal layers. Based on the presence of malignant elements they are categorized into mature and immature teratomas. The types of teratomas vary by the site of the tumor and have been reported more frequently in females displaying a bimodal incidence with the first peak between birth and 4 years of age, and the second peak at the onset of puberty. Congenital teratomas are usually extragonadal and histologically benign with a mortality of 50 percent if the

teratoma is diagnosed prenatally secondary to excessive uterine enlargement or polyhydramnios [6]. We have 3 cases of teratoma in different site location. These masses were retroperitoneal, ovarian and cervical teratomas with age 6 months, 4 years, and 8 months old respectively and all of the cases are female.

Immature teratomas are rare malignant germ cell tumors accounting less than 1% of all ovarian tumors and 20% of malignant ovarian germ cell tumors [7]. Immature teratoma contain varying quantities of neuroectodermal or blastemal tissues and may be graded by the quantity of immature neuroglial tissue. Immature teratomas have been mostly reported in the ovaries of young females, and the diagnosis of these tumors is based mainly on the pathological evaluation of the tumor tissue. A previous immunohistology study investigating immature teratoma tissue reported the presence of partial neuroendocrine differentiation of immature origin [8]. Grading on immature teratomas developed by O'Connor divided into 3 grades. Grade 1 is tumor with rare foci of immature neuroepithelial tissue that occupy < 1 low power field (40x) in any side (low-grade), grade 2 is tumors with similar elements, occupying 1-3 power fields (40x) in any slide (high-grade), and grade 3 is tumors with large amount of immature neuroepithelial tissue occupying > 3 low power field (40x) in any slide (high-grade) [3]. We had one case of grade II ovarian immature teratoma that occupied 1-3 low power fields (40x) in any slide and one case of grade III retroperitoneal immature teratoma occupied > 3 low power fields (40x) in any slide.

Lee et al, 2014 reported germ cell tumors often occur in infants, with the sacrococcygeal region, gonads, and mediastinum as the most common sites. As for teratoma, they may arise from any organ, but the majority are found in the ovary, testis, sacrococcygeal region and mediastinum. Ovarian teratoma is the most common teratoma found in children. Incidence is about 1% of all ovarian cancers and 20% of malignant germ cell tumors. It is rapidly growing malignant tumor that occur in children and young adults. To diagnose ovarian teratoma we do biopsy and pathological anatomy as a gold standard [1,3]. Retroperitoneal teratoma is rare and account for approximately 2-5% of all pediatric teratomas, constitute 3.5-4% of all germ cell tumors in children [9]. According to Anilkumar et al, 2013, incidence of retroperitoneal teratoma is bimodal with peaks in the first 6 months of life and in early adulthood. The majority are benign mature and immature teratomas, whereas malignancies occur in less than 15% of cases [9]. Retroperitoneal teratoma grow rapidly, often invading adjacent tissue to cause serious symptoms and transfer trough the blood and lymph vessels. Retroperitoneal immature teratoma is challenging to diagnose. It is also difficult to differentiate retroperitoneal immature teratoma from retroperitoneal neurogenic and yolk sac tumors, which occurs mostly in the axis of the body. The present study provides additional information on the occurrence of this rare tumor in infants. To diagnose retroperitoneal teratoma we need to do physical examination and confirmed by abdominal CT scan and pathological anatomy [8]. We have one case of retroperitoneal teratoma with the symptom in this patient was abdominal mass that noticed after birth and progressively enlargement and diagnosed with based on pathological anatomy from biopsy. This is the first and the only one case of retroperitoneal teratoma in our center until now.

Immature teratoma of the head and neck teratoma are extremely rare. These tumors are generally rare with an incidence one in 4,000 live births, although those in the head and neck make up less than 2% of cases. Only 5% of all teratomas occur in the head and neck region, predominantly in the cervical, nasopharynx, face, and orbit. The reported incidence of cervical teratomas ranges from 2.3 to 9.3% of the total. Cervical teratomas in children are almost always benign but locally aggressive. They can present with respiratory distress and immediate excision is required. Teratomas of the head and neck are interesting because of their obscure origin, bizarre microscopic appearance, unpredictable behavior and often dramatic clinical presentation [10]. Clinically, a cervical teratoma appears as a large single mass, although multiple lesions may occur. Airway obstruction is the main complication and is related to the size and site of the lesion occurring in 80% to 100% of cases. The diagnosis can be made in utero on ultrasonography in pregnancy. But if the mass is found after birth, ultrasonography, computed tomography, and MRI are important for determining the extension, involvement of adjacent structures, and helps in planning surgery [11]. Marina et al. found in a retrospective study of seventy-three children with extracranial immature teratomas that more than 85% of patients can be effectively treated with surgical resection alone and close observation. Cervical teratoma with intracranial immature teratoma is a serious case and need a urge to therapy. The mass can aggressively spread into other intracranial sites and worsen the prognosis [12]. We have one patient with the symptom was mass on neck that noticed within one month after birth and progressively enlarge until 8 months, there was a feeding difficulty, but no difficult to breath and no other respiratory symptom and diagnosed was confirmed with imaging (Head and Neck CT Scan), and from fine needle aspiration biopsy revealed a teratoma, we could not differentiate neither immature nor mature teratoma. This case is the first and the only case of cervical teratoma in our center.

The laboratory examination such as Alpha-fetoprotein is one of diagnostic tools for teratoma. Alpha-fetoprotein (AFP) is a glycoprotein produced by the yolk sac and the liver during fetal development. Serum AFP level is increased in primary liver tumors, and germ cell tumors and immature teratomas (GCT/IT). In clinical settings, AFP has been used as tumor marker for diagnosis, evaluation of treatment efficacy, and post therapy surveillance of AFP-producing tumors.

While elevated AFP levels are specific for the diagnosis of GCTs, serum AFP has not been explored because baseline AFP levels are elevated within neonates and children. In our cases, the AFP of cervical teratoma was high and lead into worst prognosis [13].

There is no consensus on the management of patients with immature teratoma. Significant different exist between pediatric and adult groups about the necessity and utility whether chemotherapy for patients with higher grade or stage disease. Norrris et al reported 18% recurrence rate for grade 2 tumors and 70% recurrence rate for grade 3 tumors, from this result they recommend using adjuvant chemotherapy for grade 2 and 3 tumors [14]. Chemotherapy will be given within 2-5 cycles based on grade of GCTs. Adjuvant chemotherapy was contained of Cisplatin, Etoposide and Bleomycin. The two of this chemotherapy (cisplatin and etoposide) can improve the 5 year survival rate 83.3%. But, Lopes et all reported for selected patients, complex three-agent regimens (cisplatin, etoposide and bleomycin) may not be necessary to achieve long-term survival, even for some patients with advanced disease [15]. All of patients were planned to get three regimens such as cisplatin, etoposide, and bleomycin. Two of them showed the good sign after doing tumor resection and finished the chemotherapy within 10-19 weeks. There was no sign of residual mass anymore in CT Scan evaluation. But one case, that is a cervical teratoma did not complete the chemotherapy and surgery yet.

The prognosis of teratoma is favorable with an 80-100% survival reported after surgical excision of the tumor and treatment of any recurrence. However, the clinical outcome of immature teratoma is highly dependent upon the grade and the treatment. Studies have shown that higher grade correlates to a poorer prognosis of cancer [16]. Adjuvant chemotherapy was not given in the index case as being a neonate and there was no tumor spillage intraoperatively. However, for incomplete surgical excision and for recurrence patient should receive 2-5 cycles of platinum-based chemotherapy. To conclude, excision of large retroperitoneal teratoma in a neonate can be a difficult in surgical endeavor, long-term outcome must be evaluated very closely [17]. Two cases after doing resection, they finished adjuvant chemotherapy for 10-19 weeks, the chemotherapy was contained Cisplatin, Etoposide and Bleomycin. One case is difficult to do any resection due to the risk of massive bleeding and the chemotherapy have done yet. Two patients who undergone surgery and chemotherapy showed a good response after resection and chemotherapy until now. There were no residual mass and other symptom.

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#### **4. Conclusion**

We presented three cases of immature teratoma. There are retroperitoneal, ovarian, and cervical immature teratoma. Two case of this immature teratoma are exceedingly rare case 1-2% of all teratoma cases. These patients had the same symptom, the symptom was preceded by an enlargement mass at sites. Two cases were noticed after birth and progressively enlarge within several months, one case noticed when the patient had a abdominal pain. We diagnosed this patient from history taking, physical examination, laboratory, pathological anatomy, and imaging. After diagnosis was established, we performed surgery and adjuvant chemotherapy for 2-5 cycles. Two patients were undergone surgery and adjuvant chemotherapy such as cisplatin, etoposide and bleomycin showed a good result, no residual mass and fully remission. But unfortunately, one patient with cervical teratoma have not undergone surgery and chemotherapy yet. We observed our patients until now, there were no new symptom for those who already undergone surgery and chemotherapy.

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#### **Compliance with ethical standards**

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##### *Disclosure of conflict of interest*

There is no conflict of interests. The author reports no conflicts of interest in this work. By this statement, all authors who consist of Ni Putu Indah Kusumadewi Riandra, Ketut Ariawati, Anak Agung Ngurah Ketut Putra Widnyana, Luh Putu Iin Indrayani Maker, I Gusti Ayu Ari Kusumawati have no conflict of interest regarding this manuscript publication.

##### *Statement of informed consent*

Informed consent was obtained from the patient whose data mentioned in the study.

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