

# Clinical Practice Guidelines For Sacrococcygeal Teratomas

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# Preface

Sacrococcygeal teratoma is a relatively rare disease. Although it is a benign tumor by nature, with a tendency towards good prognoses, in clinical practice, sacrococcygeal teratomas vary widely, including mild cases, significantly large cases leading to heavy bleeding, high-output heart failure and DIC, as well as severe and fatal cases. In addition, even after acute phase and tumor resection, some cases may experience recurrence, malignant conversion and defecation disorders, urinary disorders, movement disorders of the lower limbs, etc. in the long term.

However, because of the rarity of this disease, there have been no clear medical guidelines as of yet, with very few opportunities to encounter this disease not only for pediatricians, obstetricians and gynecologists, but also for pediatric surgeons. Therefore, in the event of the actual occurrence of this disease, general practitioners other than experts currently lack information such as what conditions are risk factors of the vital prognosis, selection of the delivery method, treatment approaches, and precautions for follow-up. For further proper medical policy, it was imperative to establish appropriate severity classification and clinical practice guidelines.

Regarding this disease, a previous study exists, "Research for Understanding the Realities and Establishing Guidelines of Fetal Sacrococcygeal Teratomas" (H23- Intractable-General-042), in which a national survey was conducted on prenatal diagnosis cases among major institutions of pediatric surgery. In this study, a development group for the clinical practice guidelines for sacrococcygeal teratomas was organized as a group within "Research for establishing guidelines for rare and intractable gastrointestinal diseases, spanning childhood to the transition phase" (H26- Intractable, etc. (Intractable)-General-045: principal investigator: Tomoaki Taguchi), with the aim of establishing clinical guidelines for sacrococcygeal teratomas and information disclosure, based on the results of previous studies.

Recently, improved outcomes of perinatal treatment for sacrococcygeal teratomas and the long-term survival of child patients have been achieved, with the occurrence of complications during the period after treatment clinically coming to the fore. Under such circumstances, the development of these guidelines is the first attempt in Japan, having huge clinical value and significance in terms of medical policies and potentially leading to the improved prognosis of child patients along with the efficient use of medical economics.

It is our desire to have these guidelines serve as a reference to all doctors engaging in medical practice for this disease in addition to contributing to improvement of the prognosis and quality of life of this disease.

Finally, I would like to show my deepest appreciation to the cooperators on the Taguchi team who were responsible for the guidelines and provided substantial effort and advice in creating these guidelines.

November 2016

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# Section1. Introduction

## Section1. Guidelines summary

1. **CQ 1: What are the risk factors related to the vital prognosis of sacrococcygeal teratomas?**

Recommendation: Risk factors related to the vital prognosis of sacrococcygeal teratomas reportedly include tumor size and growth rate, tumor characteristics and tissue type, complications of fetal edema and heart failure, early delivery, etc. It is recommended to pay attention to the existence of these risk factors when planning treatment for sacrococcygeal teratomas.

2. **CQ 2: Will the prognosis be improved if a caesarean section is performed against tumor lesions outside the pelvis?**

Recommendation: For tumor lesions outside the pelvis, it is reasonable to consider caesarean section depending on the size thereof in order to avoid tumor collapse, tumor hemorrhage, and delivery difficulty

3. **CQ 3: In the surgical treatment for sacrococcygeal teratomas, is the pretreatment of tumor feeding vessels effective?**

Recommendation: In surgical treatment for blood flow-rich sacrococcygeal teratomas, pretreatment of nutrient vessels from the median sacral artery and the internal iliac artery may be considered.

4. **CQ 4: Is IVR useful as an adjunctive treatment?**

Recommendation: Although the IVR for the sacrococcygeal teratomas facilitates tumor removal and may reduce the amount of bleeding at the time of removal, there have been few cases and skilled technique is required for the procedure. Therefore, we recommend that the feasibility of the procedure at the facility be thoroughly examined in advance.

5. **CQ 5: What kinds of tests are recommended for follow-ups on recurrence after treatment?**

Recommendation: While the risk of recurrence of malignant teratomas is high, it should be noticed that even mature or immature teratomas may become malignant and recur. AFP measurements are recommended for early detection of malignant recurrence. It is necessary to conduct follow-ups for three years after the end of treatment.

6. **CQ 6: What long-term complications (sequelae) may occur after treatment?**

Recommendation: In newborns and infants, even sacrococcygeal teratomas can be completely removed, with long-term complications often occurring such as defecation disorders, dysuria, lower limb movement disorders, and dysmorphia of wounds. It is recommended to provide these facts to patients/families before determining the treatment policy.

## **Section 2. List of terminology and abbreviations**

### 1. List of terminology

**Teratoma** : one kind of germinoma. Well-differentiated germinomas with diploblastic or triploblastic components. It occurs primarily in the gonads, but may also originate from aberrant germ cells that migrate from the yolk sac to the gonads during the process of generation, occurring throughout the body (mostly on the sagittal plane). Common sites include the genital organs, mediastinum, retroperitoneum, sacrococcygeal region, and central nerve. Mature teratomas have highly differentiated and mature tissue components, while immature teratomas have various degrees of immaturity in each component, similar to fetal tissue.

**Altman Classification** : Classification of the occurrence sites of sacrococcygeal teratomas of the 405 cases collected from facilities participating in the Surgical Section of the American Academy of Pediatrics, published by Altman et al. in 1974.

**Radiofrequency ablation (RFA)** : Percutaneously injecting an electrode probe into a tumor, distributing a radio wave (450 kHz), and generating heat energy that causes thermal coagulation necrosis of the tumor tissue.

### 2. Abbreviation list

**IVR**: interventional radiology. Treatment using images. It is a part of radiology and one involving minimally invasive medical treatments using diagnostic imaging equipment, including transcatheter arterial embolization and radiofrequency ablation.

**AFP**: alpha-fetoprotein. Glycoprotein produced in the yolk sac in fetal life, with production ceasing at birth. It is used as a tumor marker, exhibiting high values in yolk sac tumors containing yolk sac components or malignant teratomas as germinomas. It exhibits tens of thousands to hundreds of thousands ng/mL at birth, tens of thousands times the baseline values of adults, and drops to hundreds to 10,000 ng/ml 30 days after birth. Thereafter, it continues decreasing, falling to less than 10 ng/mL by the age of 4 or 5, which is similar to that of adults. Therefore, if a germinoma is suspected in infancy, it is necessary to compare AFP values in accordance with their age.

# Chapter 2. SCOPE

## Section 1. Basic characteristics of the disease topic

### 1. Clinical characteristics

Sacrococcygeal teratomas are teratomas developing from the tip of the sacrum, a tumor that protrudes outward from the buttocks or develops into the pelvic cavity/abdominal cavity, which can take various forms such as a solid or cyst. Teratomas originate from cells with multilineage potential located at the tip of the coccyx (Hensen's node) and are defined as tumors containing components derived from all germ layers including the endoderm, mesoderm, and ectoderm. Because it contains components derived from the three germ layers, it may contain various tissues such as bone, teeth, hair, fat, nerve tissue, airway tissue, digestive tract epithelium, and skin. In some cases, the tumors are originally benign but develop into large ones, leading to high-output heart failure and DIC, and even death.

The Altman classification is used for classification according to the occurrence site of sacrococcygeal teratomas, including the following types:

Type I: Most of the tumor constitutes components outside the pelvis

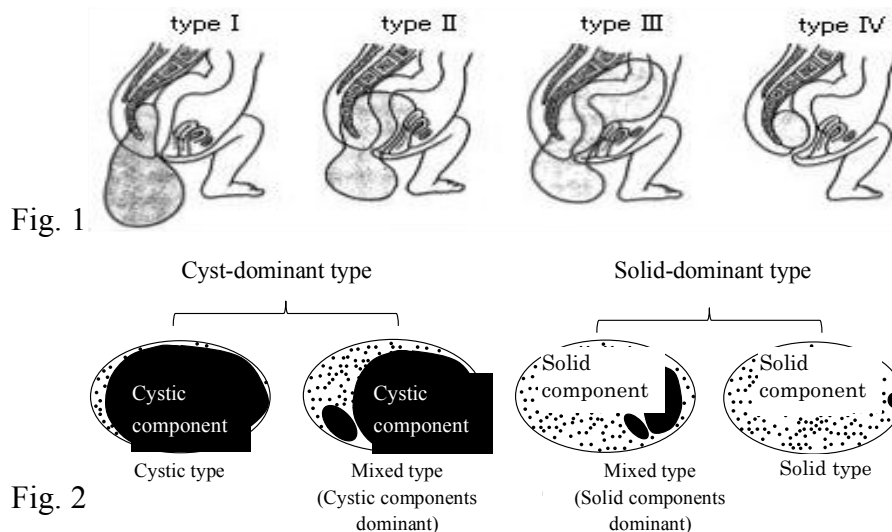
Type II: Although there is development inside the pelvic cavity, components outside the pelvis are larger

Type III: Although there is development outside the pelvis, components inside the cavity of the pelvis and abdomen are larger

Type IV: There is no development outside the pelvis, only including components inside the cavity of the pelvis and abdomen

(Fig. 1).

According to the study by the Kitano group-Taguchi group in 2009-2011, the macroscopic form of this disease can be classified into two types and four subtypes, including the cyst-dominant type (cystic type, mixed type with cystic components dominant) and the solid-dominant type (mixed type with solid components dominant, solid type) (Fig. 2). Histopathologically, it is classified into mature teratomas whose components have all matured and differentiated, premature teratomas containing immature components, and yolk sac tumors containing malignant components. Sometimes hybrids of these types may occur.



## 2. Epidemiological characteristics

They are said to occur in 1 case out of 40,000 births. The male-female ratio is approximately 1:3, more frequently occurring in girls. The occurrence of sacrococcygeal teratomas is most frequent among teratomas diagnosed during the neonatal period, with most cases diagnosed at the time of birth being mature teratomas/immature teratomas. However, the occurrence of yolk sac tumors which are malignant teratomas after one year of age is high, reportedly occurring at a rate of 75% or more.

The symptoms include the tumor growing outward from the buttocks or into the pelvic cavity. The tumor may cause compression on the ureter, bladder, and rectum, resulting in urinary retention or constipation, or movement disorders of the lower limbs. In cases detected in the fetal period, a solid tumor rich in blood flow may become a fetal edema due to high-output heart failure, possibly resulting in an intrauterine fetal death or early delivery by urgent caesarean section. With malignant teratomas, in addition to defecation disorders/urinary disorders, inguinal lymph node enlargement, development into the spinal canal, and metastasis to multiple organs may be observed.

## 3. Overall flow of medical examinations

The following two are the diagnostic criteria for this disease:

- (1) Upon imaging diagnoses (including prenatal examination) such as by CT, MR, ultrasonography or surgical findings, a solid or cystic tumor is found to occur in the sacrococcygeal site without a connection to the neural tube, with development into the abdominal cavity or proptosis toward the buttocks also found.
- (2) Based on the histological diagnosis of tumors excised at surgery, a tissue type of either a mature teratoma, immature teratoma, or malignant teratoma can be found.

For some reason, if histological diagnosis is difficult due to surgery, a definite diagnosis can be made if (1) is met.

For mature teratomas and immature teratomas, surgical resection is carried out. In cases of Altman type I, many patients undergo resection approaching from the buttocks, while peritoneotomy is also used in patients with large amounts of intraabdominal components. With gigantic solid masses, the risk of bleeding is high. It is useful to first ligate the median sacral artery, which is a nutrient blood vessel. With yolk sac tumors, chemotherapy such as BEP therapy may be carried out first, followed by surgical resection.

From the examination of cases of sacrococcygeal teratomas discovered in the fetal period in Japan, fetal edema and high output heart failure were found, with 12% dying in the perinatal stages. On the other hand, the death rate after infancy makes up 2% of the total, indicating that deaths during the time period after treatment are relatively rare. However, it has been reported that recurrence occurred in 8% of teratomas removed during neonatal infancy and infancy, suggesting the necessity of careful follow-up. In addition, for malignant sacrococcygeal teratomas, a 4-year survival rate of approximately 90% has been reported. With this disease, it has been reported that defecation disorders/urination disorders/movement disorders of the lower limbs remain in approximately 15% of patients following resection, so sufficient care is necessary in regards to these disorders.

The severity criteria of sacrococcygeal teratomas are as follows:

### (1) Mild cases

Those definitively diagnosed with this disease by the diagnostic method described above, surviving more than 90 days and not falling under any item of a) to d) of (2)

### (2) Severe cases

Those definitively diagnosed with this disease by the diagnostic method described above, surviving more than 90 days and falling under any of the following items a) to d)

a) Those with dysuria

b) Those with bowel movement disturbance

b) Those with movement disorders in the lower limbs

d) Those with mental retardation/motor retardation/hypoxic encephalopathy/other central nervous disorder

(3) Most severe cases

Those definitively diagnosed with this disease by the diagnostic method described above, resulting in fetal death due to high-output heart failure, fetal edema, massive bleeding, DIC, etc., or surviving less than 90 days.

## **Section 2. Coverage of the clinical practice guidelines**

### 1. Title

Clinical practice guidelines for sacrococcygeal teratoma

### 2. Objective

To make the rare disease sacrococcygeal teratoma better known, share information on the disease concept, diagnostic criteria, and severity assessment, and provide information for decision making in terms of medical services (diagnosis, treatment).

### 3. Topic

Sacrococcygeal teratomas have a relatively high mortality rate in the neonatal period, involving the possibility of postoperative complications and recurrence occasionally accompanied by malignantization. Due to the low occurrence frequency, the sample size is small even on a global scale. Therefore, there is little evidence of high-quality treatment that could be applied to patients, nor standardized treatment policies. In most cases, treatment has been based on the experience of individual facilities and physicians. This is why we developed these guidelines. Because it is a rare disease, it is vital to pay attention not to form a consensus biased toward the opinion of a few experts.

### 4. Target users and facilities

#### **【Users】**

(1) Healthcare professionals who will encounter this disease in the early stages (general practitioners such as obstetrics, pediatrics, etc.)

(2) Healthcare professionals at secondary and tertiary medical facilities that provide primary medical services for this disease such as obstetricians, neonatologists, pediatricians and pediatric surgeons



## 【Facilities】

General practitioners such as maternity wards and pediatrics, perinatal care facilities, comprehensive perinatal medical centers, regional perinatal medical centers, neonatal training institutes of the Japan Society of Perinatal and Neonatal Medicine, facilities accredited by the Japan Society of Pediatric Surgeons, education-related facilities of the Japan Society of Pediatric Surgeons, primary, secondary, tertiary medical care facilities such as training facilities for physicians certified by the Japanese Society of Pediatric Hematology/Oncology

### 5. Relationship with existing guidelines

No guidelines concerning sacrococcygeal teratomas exist in Japan or other countries.

### 6. Important clinical issues

【Important clinical issue 1】 Pathology (preoperative complications and risk factors)

【Important clinical issue 2】 Diagnosis

【Important clinical issue 3】 Treatment (delivery method, operative procedure, adjuvant therapy)

【Important clinical issue 4】 Prognosis (postoperative recurrence/complications in long-term prognoses)

### 7. Coverage of the clinical practice guidelines

(1) Sacrococcygeal teratomas in infants

(2) Treatment for patients who have been definitively diagnosed with this disease

(3) Prenatal diagnosis, perinatal care management, preoperative management, IVR, surgical therapy, postoperative management

(4) Complications, long-term follow-up, prognosis

### 8. Clinical questions (CQ)

**CQ 1: What are the risk factors related to vital prognosis?**

**CQ 2: Will the prognosis be improved if a caesarean section is performed against tumor lesions outside the pelvis?**

**CQ 3: In the surgical treatment, is the pretreatment of tumor feeding vessel effective?**

**CQ 4: Is IVR useful as an adjunctive treatment?**

**CQ 5: What kinds of tests are recommended for follow-ups on recurrence after treatment?**

**CQ 6: What are the long-term complications (sequelae) after treatment?**

# Chapter 3. Recommendations

## Section 1. CQ1

<b>CQ 1</b>	<b>What are the risk factors related to vital prognosis of sacrococcygeal teratoma?</b>
Recommendations	Risk factors related to the vital prognosis of sacrococcygeal teratomas reportedly include tumor size and growth rate, tumor characteristics and tissue type, complications of fetal edema and heart failure, early delivery, etc. It is recommended to pay attention to the existence of these risk factors when planning treatment for sacrococcygeal teratomas.
Strength of evidence	<input type="checkbox"/> A (strong) <input type="checkbox"/> B (medium) <input type="checkbox"/> C (weak) <input checked="" type="checkbox"/> D (very weak)
Strength of recommendation	<input checked="" type="checkbox"/> Strongly Recommend "Implementing" <input type="checkbox"/> Weakly Recommend (Suggest) "Implementing" <input type="checkbox"/> Weakly Recommend (Suggest) "Not Implementing" <input type="checkbox"/> Strongly Recommend (Suggest) "Not Implementing" <input type="checkbox"/> Strongly Recommend "Not Implementing" <input type="checkbox"/> No Recommendation

### Creation process of the recommendations

<p><b>【Settling of PICO】</b></p> <p>Senobotic teratomas are germinomas that develop in the sacrococcygeal site and have the highest occurrence rate among neonatal tumors. Although the prognosis for the disease has been considered to be relatively good, the prognosis of cases diagnosed before birth is not always good. A nationwide survey, from a previous study, has shown that there were many cases of death in the fetal stage or postnatal early stage, along with many cases involving severe complications. At the clinical site, one of the most Important issues is what kind of factors we should pay attention to in planning the treatment regimen. Therefore, we raised the question, "What are the risk factors related to the vital prognosis of sacrococcygeal teratomas during the neonatal and infant period?" as CQ1, setting PICO as follows.</p> <p>P: infants with sacrococcygeal teratomas under 1 year old</p> <p>I: gestational age, birth weight, fetal edema, tumor collapse, tumor bleeding, high output heart failure, disseminated intravascular coagulation, tumor size, tumor properties (solid/cyst type), tumor tissue type (immature teratomas/mature teratomas), tumor site (Altman I-II type/Altman III-IV type)</p> <p>C: Cannot be set</p> <p>O1: The vital prognosis gets worse.</p>
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### 【Literature search and screening】

Approximately 290 documents were searched for risk factors related to the vital prognosis of sacrococcygeal teratomas, 110 of which were subject to primary screening. After examination, 50 documents were subjected to secondary screening. Among these, there were no Cochrane reviews, systematic reviews, or reports on randomized controlled trials and non-randomized controlled trials. As there were 13 documents (reference 1 to 13) in which reference was made to the vital prognosis as the primary outcome and analysis on the factors listed above was conducted, in the end, we adopted these 13 references. All of them were case series studies including 6 to 97 subjects.

### 【Risk factors related to vital prognosis】

Risks related to vital prognosis can be divided into factors of the tumor itself and factors of the children. Brace et al. reported a rapid increase in tumor size in the fetal stage and onset of fetal edema in all five deaths out of eight cases<sup>1)</sup>. With regard to the growth rate of the tumor, Wilson et al. reported that the rate of mortality rises if the weekly growth rate exceeds 150 cm<sup>3</sup>/week<sup>2)</sup>. In addition, Shue et al. and Rodriguez et al. reported that the larger the tumor volume to fetal weight ratio (TFR), the worse the prognosis<sup>3)4)</sup>. All patients with TFR of 0.12 or more had fetal edema<sup>4)</sup>. Moreover, the spread of vascular distribution within the tumor and the amount of solid components have reportedly been correlated with the mortality rate<sup>5)6)</sup>. Perrelli et al. reported that 2 deaths out of 17 cases were malignant tissue type<sup>7)</sup>. Yoneda et al. reported recurrence in 8 of 31 immature teratomas and 2 recurrences out of 48 mature teratomas<sup>8)</sup>. De Backer et al. reported that 6 deaths out of 70 cases were immature teratomas or yolk sac tumors<sup>9)</sup>. As molecular-biological research, Addeo et al. also reported that high expression intensity and mutation of Bax protein in tumors are correlated with poor prognosis<sup>10)</sup>. On the other hand, it has been reported that the Altman classification, which is the morphological classification of tumors, does not correlate with prognosis<sup>11)</sup>. From these facts, (1) tumor size and growth rate, along with (2) tumor properties and tissue type, may be risk factors of tumors related to vital prognosis.

On the other hand, as risk factors among children, Okada et al. reported that heart failure and fetal edema were observed in 1 death out of 6 patients<sup>12)</sup>, while Hedrick et al. reported 3 of 5 fetal deaths had heart failure and fetal edema<sup>13)</sup>. Benachi et al. also reported that 11 patients died among 21 patients with signs of heart failure and a tumor diameter exceeding 10 cm<sup>5)</sup>. In addition, Usui et al. reported that the mortality rates of those of gestational age less than 28 weeks, 28 weeks to 31 weeks, 32 weeks to 36 weeks, and more than 37 weeks were respectively 60%, 38%, 11% and 0%<sup>6)</sup>, while Hedrick et al. reported that the average gestational age of the seven cases of newborn death was 28.6 weeks<sup>13)</sup>. From these facts, we assume that 1) complication of fetal edema, 2) complication of heart failure, and 3) early delivery, may be risk factors among children in relation to vital prognosis.

## Section 2. CQ2

<b>CQ 2</b>	<b>Will the prognosis be improved if a caesarean section is performed against tumor lesions outside the pelvis?</b>
Recommendations	For tumor lesions outside the pelvis, it is reasonable to consider caesarean section depending on the size thereof to avoid tumor collapse, tumor hemorrhage, and delivery difficulty
Strength of evidence	<input type="checkbox"/> A (strong) <input type="checkbox"/> B (medium) <input type="checkbox"/> C (weak) <input checked="" type="checkbox"/> D (very weak)
Strength of recommendation	<input type="checkbox"/> Strongly Recommend "Implementing" <input checked="" type="checkbox"/> Weakly Recommend (Suggest) "Implementing" <input type="checkbox"/> Weakly Recommend (Suggest) "Not Implementing" <input type="checkbox"/> Strongly Recommend (Suggest) "Not Implementing" <input type="checkbox"/> No Recommendation

### Creation process of the recommendations

<p><b>【Settling of PICO】</b></p> <p>P: Infant sacrococcygeal teratomas with extrapelvic tumors (Altman types I to II)</p> <p>I: delivery by cesarean section (scheduled)</p> <p>C: delivery not by cesarean section (scheduled)</p> <p>O1: improvement in vital prognosis</p> <p>O2: decrease in tumor bleeding</p> <p>O3: decrease in tumor collapse</p> <p>O4: decrease in postoperative complications</p>
<p><b>【Literature search and screening】</b></p> <p>Regarding the usefulness of performing a caesarean section on a fetus with extrapelvic lesions, 106 documents were included in the primary screening. 44 documents were included in the secondary screening to obtain 14 documents in the end. Eleven out of the 14 documents were case series/case reports, while three were review articles.</p> <p><b>【Results of qualitative review】</b></p> <p><b>O1: improvement in the vital prognosis</b></p> <p>Comparison of caesarean delivery and vaginal delivery: While there are no reports comparing caesarean delivery and vaginal delivery with respect to vital prognosis, several studies have reported on problems with vaginal delivery due to sacrococcygeal teratomas. The problems include the fact that extrapelvic lesions cause fetal malposition or hinder the progress of labor, along with the fact that tumors may collapse at delivery, leading to bleeding into the tumor and blood loss in the fetus<sup>1-5</sup>). Although these papers are case series and case reports, each of them recommend caesarean delivery. On the other hand, although similar</p>

problems exist, it has been reported that vaginal delivery is considered depending on the tumor size (less than 5 cm)<sup>6) 14)</sup>. It has also been reported that caesarean section caused tumor damage leading to death due to bleeding<sup>7)</sup>, suggesting the necessity to examine methods to prevent bleeding from tumors such as adding a new twist to uterotomies. We believe that the problem at delivery having the greatest impact on the prognosis of the fetus is blood loss due to tumor damage. While caesarean section delivery may potentially reduce such risks, it is unknown whether or not it may improve the vital prognosis.

Comparison between scheduled caesarean section and emergency caesarean section: we examined the vital prognosis of sacrococcygeal teratomas diagnosed at the fetal stage in Japan<sup>7)</sup>, by comparing the delivery method between 11 cases of postnatal death and 71 cases of survival. The results showed that the proportion of emergency caesarean sections was significantly higher in cases of postnatal death than in surviving cases (72.7% vs 29.9%), while that of scheduled caesarean sections was significantly lower (18.2% vs 48.1%). In many cases, emergency caesarean sections were performed for fetal indications requiring delivery, due to fetal dysfunction such as fetal edema and tumor hemorrhage, resulting in more frequent deaths. It may be necessary to take appropriate medical intervention at the stage before emergency caesarean sections.

Prognostic factors of fetuses: it has been reported that important fetal prognostic factors in sacrococcygeal teratomas include the number of weeks pregnant at delivery, fetal cardiac dilatation, fetal edema, signs of fetal heart failure<sup>8-11)</sup>. According to reports in Japan, postnatal death cases have the following characteristics, compared to surviving cases: 1) gestational age (week) at diagnosis is significantly smaller, 2) the number of weeks pregnant at delivery is significantly smaller, 3) signs of fetal heart failure are significantly more frequent, 4) the number of solid-dominant tumor types and solid tumor types is significantly larger, 5) the occurrence of tumor collapse and tumor bleeding at birth is significantly more frequent, 6) the tumor diameter was significantly larger, and 7) the number of immature teratomas was significantly larger in terms of the pathology<sup>7)</sup>. Since some of these items can be found before birth by ultrasonography, etc., the prognosis may be improved in some cases by medical intervention before abnormal findings appear.

Selection of delivery method/timing of delivery: the improvement of diagnostic techniques has contributed to the increase in prenatal diagnosis and therefore the accumulation of information. Based on such reports, algorithms for prenatal management of fetal sacrococcygeal teratomas have been proposed<sup>12)</sup><sup>13)</sup>. In some of these algorithms, fetal treatment is also taken into consideration regarding the continuation of pregnancy when the number of weeks (pregnant) is less than 28, wherein prematurity is a major problem. Going forward, it is necessary to examine the usefulness of these algorithms by accumulating further reports.

In summary, when caesarean section is performed at an appropriate time for extrapelvic tumor lesions, it may reduce the risk of tumor damage and improve the prognosis. However, vital prognoses are affected by many other factors, making it hard to conclude that it can be improved by caesarean section alone.

**O2: decrease in tumor bleeding**

**O3: decrease in tumor collapse**

We could find no documents comparing the amount of bleeding during vaginal delivery and caesarean section. As mentioned above, the problems with transvaginal delivery due to extrapelvic lesions include abnormal progress of labor, tumor collapse, and bleeding into the tumor. According to the case series by Holzgreve et al., 3 of 5 newborn deaths were attributed to tumor collapse during vaginal delivery<sup>3)</sup>. From these facts, each reference recommends caesarean delivery. However, some references report that vaginal delivery can be performed for those with a small tumor diameter (less than 5 cm)<sup>6) 13) 14)</sup>. In a nutshell, we believe that tumor collapse and tumor bleeding may be reduced by selective caesarean section for those with large tumors, while vaginal delivery may be performed without causing tumor damage depending on the size of the tumor.

**O4: decrease in postoperative complications**

There are no reports regarding whether or not scheduled caesarean delivery will reduce postoperative complications, compared to delivery not by scheduled caesarean section. In general, the risk of emergency caesarean section is higher.

From the above, although caesarean section may reduce the risk of tumor damage and delivery difficulties, vital prognoses are affected by many other factors, making it hard to conclude that it can be improved by caesarean section alone (**O1**). We believe that tumor collapse and tumor bleeding may be reduced by selective caesarean section for those with large tumors (**O2, O3**). The contribution of caesarean sections to postoperative complications is unknown (**O4**). However, in the sense that caesarean sections reduce the risk at delivery, the selection of caesarean section for large tumors is considered a clinically reasonable choice.

1.

### Section 3. CQ3

<b>CQ 3</b>	<b>In the surgical treatment of sacrococcygeal teratomas, is the pretreatment of tumor feeding vessel effective?</b>
Recommendations	In surgical treatment for blood flow-rich sacrococcygeal teratomas, pretreatment of nutrient vessels from the median sacral artery and the internal iliac artery may be considered.
Strength of evidence	<input type="checkbox"/> A (strong) <input type="checkbox"/> B (medium) <input type="checkbox"/> C (weak) <input checked="" type="checkbox"/> D (very weak)
Strength of recommendation	<input type="checkbox"/> Strongly Recommend "Implementing" <input checked="" type="checkbox"/> Weakly Recommend (Suggest) "Implementing" <input type="checkbox"/> Weakly Recommend (Suggest) "Not Implementing" <input type="checkbox"/> Strongly Recommend (Suggest) "Not Implementing" <input type="checkbox"/> No Recommendation

#### Creation process of the recommendations

<p><b>【Settling of PICO】</b></p> <p>In the treatment strategy for neonatal sacrococcygeal teratomas, we assume that the intraoperative amount of bleeding greatly influences on the prognosis of the patient. Therefore, for tumors rich in blood flow, if it is possible to reduce the amount of intraoperative bleeding by blocking the blood flow of tumor feeding vessels from the median sacral artery and the internal iliac artery prior to tumor resection, we believe the prognosis of patients may be improved, raising the question "In the surgical treatment for sacrococcygeal teratomas, is pretreatment of tumor feeding vessels effective?" as CQ3 and setting PICO as follows.</p> <p>P: infants with sacrococcygeal teratomas under 1 year old</p> <p>I: Pretreatment of tumor feeding vessels</p> <p>C: No pretreatment of tumor feeding vessels</p> <p>O1: improvement in vital prognosis (benefit)</p> <p>O2: decrease in amount of bleeding (benefit)</p> <p>O3: decrease in postoperative complications (benefit)</p> <p>O4: increase in postoperative ileus (harm)</p>
<p><b>【Literature search and screening】</b></p> <p>Among 180 searched documents, 47 documents were included in the secondary screening. After examination, 14 documents were included in the secondary screening. As a result of the secondary screening, 12 documents, excluding two mentioning the blocking of blood flow by embolization, were not Cochrane reviews, systematic reviews, randomized controlled trials, nonrandomized controlled trials, interventional studies, or observational research, indicating that an evaluation of the body of evidence cannot be done. Because all of them were case reports or case series, a qualitative review was carried out based on</p>

these 12 references (2 case series, 10 case reports).

**【Results of qualitative review】**

There have been many reports indicating that the devascularization of feeding vessels from the median sacral artery or the internal iliac artery prior to tumor resection was useful for decreasing the intraoperative amount of bleeding. As methods of devascularization, there have been reports on ligation by laparotomy<sup>1-5)</sup> as well as ligation using laparoscopy<sup>6-9)</sup>. However, despite the pretreatment of feeding blood vessels, some reports indicated that massive bleeding was observed during surgery and pretreatment was not effective<sup>4)10)</sup>. On the other hand, there have been no reports on complications related to the intraperitoneal pretreatment of tumor feeding vessels, including postoperative ileus. There have been no reports on improvement of the vital prognosis or reduction of postoperative complications due to pretreatment. With respect to the amount of bleeding, the number of reports indicating the effectiveness (benefit) of pretreatment exceeded that of reports showing the ineffectiveness thereof, with no reports indicating any harm caused by pretreatment. Therefore, we believed that the pretreatment of feeding vessels from the median sacral artery or the internal iliac artery is effective. However, because all the papers were case reports or case series, it is assumed that very serious selection bias is included in the conclusion that the pretreatment of tumor feeding vessels is effective. Because the evidence level is very low and the strength of recommendation is weak, we deem it appropriate to say that the pretreatment of feeding vessels "may be taken into consideration."



## Section 4. CQ4

CQ 4	Is IVR useful as an adjunctive treatment?
Recommendations	Although the IVR for sacrococcygeal teratomas facilitates tumor removal and may reduce the amount of bleeding at the time of removal, there have been few cases and skilled technique is required for the procedure. Therefore, we recommend that the feasibility of the procedure in the facility be thoroughly examined in advance.
Strength of evidence	<input type="checkbox"/> A (strong) <input type="checkbox"/> B (medium) <input type="checkbox"/> C (weak) <input checked="" type="checkbox"/> D (very weak)
Strength of recommendation	<input type="checkbox"/> Strongly Recommend "Implementing" <input checked="" type="checkbox"/> Weakly Recommend (Suggest) "Implementing" <input type="checkbox"/> Weakly Recommend (Suggest) "Not Implementing" <input type="checkbox"/> Strongly Recommend (Suggest) "Not Implementing" <input type="checkbox"/> No Recommendation

### Creation process of the recommendations

<p><b>【Settling of PICO】</b></p> <p>If the teratomatous teratoma has an abundant blood flow and the tumor diameter is 10 cm or more, intraoperative bleeding at the time of resection affects the prognosis of infant patients. Therefore, we believe that if intraoperative bleeding can be reduced by carrying out embolization of the feeding vessels by IVR prior to resection surgery for tumors with abundant blood flow, the prognosis of infant patients may be improved. We set CQ 4 as “Is IVR useful as an adjunctive treatment?”, and set up PICO as follows:</p> <p>P: infants with sacrococcygeal teratomas under 1 year old</p> <p>I: IVR is carried out</p> <p>C: IVR is not carried out</p> <p>O1: improvement in the vital prognosis</p> <p>O2: decrease in the amount of bleeding (benefit)</p> <p>O3: decrease in postoperative complications</p> <p>O4: complications occur due to IVR</p>
<p><b>【Literature search and screening】</b></p> <p>We found approximately 211 documents on the effectiveness as adjunctive treatment of IVR (Interventional Radiology), 16 of which were subject to primary screening. After examination, 11 documents were included in the secondary screening. Among them, there were no Cochrane reviews, systematic reviews, or reports on randomized controlled trials and non-randomized controlled trials. Four papers regarding IVR conducted after birth were all case reports (references 1 to 4), which were adopted in the end</p>

**【Regarding IVR】**

The IVR performed on infant patients after birth were four cases of transcatheter arterial embolization <sup>1-4)</sup>, including one case in which radiofrequency ablation (RFA) was carried out prior to birth <sup>2)</sup>, and one case in which RFA was performed as an additional treatment after embolization<sup>1)</sup>. The maximum diameter of all the tumors subject to treatment was 10 cm or more.

Regarding the four cases involving IVR, the following table shows the catheter insertion path/embolic blood vessel/embolus material/time required for the procedure/time required for the operation/intraoperative amount of bleeding.

Reference number	Catheter insertion path	Embolic blood vessel	Embolus material	Time required for the procedure (minutes)	Time required for surgery (minutes)	Intraoperative bleeding (mL)
1	Right femoral artery	Bilateral internal iliac arteries	Gelfoam suspension and liquid obstructing material	180 (including the time following RFA)	60	Unknown, there is an indication that additional hemostasis surgery is unnecessary
2	Umbilical artery	Bilateral internal iliac arteries	Unknown	Unknown	Unknown	Unknown
3	Left common carotid artery	Median sacral artery and right internal iliac artery	Gelatin sponge, median sacral artery with detachable coil embolus added	80	105	10 It was reported that intraoperative management was difficult for reasons other than bleeding
4	Left subclavian artery	Median sacral artery and right internal iliac artery	Gelatin sponge, median sacral artery with pushable coil embolus added	55	Unknown	12

In two cases, it was reported that although IVR is effective, proficient skill is required for the procedure<sup>1)3)</sup>.

**【Results of qualitative review】**

**O1: improvement in the vital prognosis**

Although there were no reports on the improvement of vital prognosis, all cases undergoing IVR are surviving <sup>1-4)</sup>. In 2 of 4 cases, it was reported that the tumor could be easily removed <sup>3)4)</sup>. On the other hand, in 1 of the 4 cases, persistent blood transfusion and hyperkalemia caused difficulty in intraoperative

management (with intraoperative cardiac arrest)<sup>3)</sup>.

**O2: decrease in the amount of bleeding (benefit)**

In 3 of 4 cases in which IVR was performed, there was little bleeding during subsequent tumor resection<sup>1) 3) 4)</sup>, with the amount of bleeding recorded as 10 mL<sup>3)</sup>, 12 mL<sup>4)</sup> in two cases.

**O3: decrease in postoperative complications**

For the 4 cases in which IVR was performed, there was no clear description that the postoperative complications were reduced, nor a description that complications were observed after surgery<sup>1-4)</sup>.

**O4: complications occur due to IVR**

In all 4 cases undergoing IVR, we could find no description of complications<sup>1-4)</sup>.

In summary, although the IVR for sacrococcygeal teratomas facilitates tumor removal and may reduce the amount of bleeding at the time of removal, there have only been case reports and skilled technique is required for the procedure. Therefore, we recommend that the feasibility of the procedure in the facility be thoroughly examined in advance.

1.

## Section 5. CQ5

<b>CQ 5</b>	<b>What kinds of tests are recommended for follow-ups on recurrence after treatment?</b>
Recommendations	While the risk of recurrence of malignant teratomas is high, it should be noted that even mature or immature teratomas may become malignant and recur. AFP measurements are recommended for early detection of malignant recurrence. It is necessary to conduct follow-ups for three years after the end of treatment.
Strength of evidence	<input type="checkbox"/> A (strong) <input type="checkbox"/> B (medium) <input type="checkbox"/> C (weak) <input checked="" type="checkbox"/> D (very weak)
Strength of recommendation	<input checked="" type="checkbox"/> Strongly Recommend "Implementing" <input type="checkbox"/> Weakly Recommend (Suggest) "Implementing" <input type="checkbox"/> Weakly Recommend (Suggest) "Not Implementing" <input type="checkbox"/> Strongly Recommend (Suggest) "Not Implementing" <input type="checkbox"/> No Recommendation

### Creation process of the recommendations

<p><b>【Settling of PICO】</b></p> <p>P: survivors undergoing surgery for sacrococcygeal teratomas (from infants (under 1 year old) to adults)  I: postoperative examination (imaging examination, tumor marker, body findings)  C: Not applicable  O1: relapse can be detected at an early stage  O2: vital prognosis after relapse is improved</p>
<p><b>【Literature search and screening】</b></p> <p>304 references regarding follow-up for post-treatment relapse were included in the primary screening. Among these, 63 references were included in the secondary screening. With 21 articles adopted as a result, a qualitative review was carried out based on seven case series studies thereamong.</p> <p><b>【Risk factors of relapse】</b></p> <p>There were no prospective clinical studies on the recurrence of sacrococcygeal teratomas, all of which were retrospective case series. According to a report from the Netherlands on the risk factors of recurrence<sup>1)</sup>, it was reported that in 173 patients, malignant and immature teratomas were compared with mature teratomas, wherein the odds ratio of malignant and immature teratomas to mature teratomas was reported to be 12.58 and 5.74, respectively, while that of incomplete resection was 6.54. However, looking only at patients under 1 year old, the target of these guidelines, there were many benign teratomas, including 79 cases of mature teratomas, 26 cases of immature teratomas, and 10 cases of malignant teratomas, wherein recurrence was found in 9 of 101 cases whose prognosis was known (8.9%). According to studies by</p>

DeBaker et al., which in some cases are thought to overlap with the above study<sup>2)</sup> (70 cases including 50 cases of prenatal diagnosis and diagnosis at birth (mature teratomas:immature teratomas:malignant teratomas = 48:11:9)), even in the cases of incomplete resection, because the risk of recurrence is not high if the stump is mature or an immature teratoma, conservative follow-up is recommended. According to a report by Rescorla et al., with accrual of cases from 15 facilities in the United States<sup>3)</sup>, among 126 patients with sacrococcygeal teratomas at age 1 or younger (mature teratomas:immature teratomas:yolk sac tumors = 80:24:11), it was reported that the recurrence rate was high, in the order of yolk sac tumors then mature teratomas, as the initial tissue type (mature teratomas:immature teratomas:yolk sac tumors = 11%: 4.2%: 33%). In addition, according to a multicenter study<sup>4)</sup> in Japan, 6 of 72 cases (8.3%) of prenatal diagnosis recurred by 16 months of age, among which 5 cases recurred with malignant alteration (4 mature teratomas and 1 immature teratoma at the initial stage). According to the US POG/CCSG's investigation on six cases of recurrence with malignant alteration from a sacrococcygeal teratoma occurring in the neonatal stage<sup>5)</sup>, it was reported that in 4 of 5 cases in which tissues could be found, micro accumulation of yolk sac tumor cells was observed. In MAKEI<sup>6)</sup>, a clinical study of germinomas in Germany, 5 of 22 cases of sacrococcygeal teratomas recurring as malignancies were diagnosed as tumors. Two of these were excised, three were followed-up, with the age in months at the time of recurrence reportedly being 12 to 26 months.

From these facts, recurrence risk factors include malignant teratomas and being positive for resection stumps in malignant cases. It should be noted that even mature teratomas and immature teratomas may recur with malignant alteration, in addition to cases with complete resection potentially recurring as well. Moreover, it is necessary to follow up until the age of three because most cases of recurrence occur by the age of two.

#### **【Tumor markers】**

There have been many reports on the measurement of AFP at follow-up for recurrence, many of which indicate high AFP levels at onset. According to Hawkins et al. (POG/CCSG)<sup>5)</sup>, AFP was increased in all six patients (100%) with recurrent malignant sacrococcygeal teratomas (218 to 32,000 ng/mL). According to Schneider et al. (MAKEI)<sup>6)</sup>, AFP was increased in 21 of 22 patients (95.4%) with recurrent malignant sacrococcygeal teratomas. In addition, Pauniahio et al.<sup>7)</sup> reported a high level of AFP (2.5-fold the median) in 33% of non-recurrent patients (6/18), with a high level of AFP in 66% of recurrent patients (4/6). In the same report, CA 19-9 rose by 6% in non-recurrent patients (1/18), while rising by 66% (4/6) in recurrent patients, indicating its effectiveness in recurrent cases of mature and immature teratomas. From these facts, AFP may be useful for follow-up of recurrence.

#### **【Image Protocol】**

Regarding images, there have been no documents that specifically examined the usefulness, shooting interval, or shooting method thereof. One report included a specific description: CT was carried out every three months for the first year and every six months for the second year<sup>6)</sup>.

## Section 6. CQ6

<b>CQ 6</b>	<b>CQ 6: What long-term complications (sequelae) exist after treatment?</b>
Recommendations	In newborns and infants, even sacrococcygeal teratomas can be completely removed, with long-term complications often occurring such as defecation disorders, dysuria, lower limb movement disorders, and dysmorphia of wounds. It is recommended to provide these facts to patients/families before determining the treatment policy.
Strength of evidence	<input type="checkbox"/> A (strong) <input type="checkbox"/> B (medium) <input type="checkbox"/> C (weak) <input checked="" type="checkbox"/> D (very weak)
Strength of recommendation	<input checked="" type="checkbox"/> Strongly Recommend "Implementing" <input type="checkbox"/> Weakly Recommend (Suggest) "Implementing" <input type="checkbox"/> Weakly Recommend (Suggest) "Not Implementing" <input type="checkbox"/> Strongly Recommend (Suggest) "Not Implementing" <input type="checkbox"/> No Recommendation

### Creation process of the recommendations

#### 【Settling of PICO】

For neonatal and infant sacrococcygeal teratomas, even for cases in which tumor resection leads to a cure, long-term complications may significantly reduce QOL. Therefore, we believe that it is important to recognize that these long-term complications may occur and take care of them through follow-ups and family life, giving the CQ "What are the long-term complications (sequelae) after treatment?" and setting up PICO as follows.

P: From infants to adults who received treatment for sacrococcygeal teratomas during infancy (under 1 year old)

I: Long-term postoperative complications

C: Not applicable

O1: Dysfunction can be found at an early stage (benefit)

O2: QOL decreases (harm)

### 【Literature search and screening】

287 references regarding long-term complications (sequelae) were included in the primary screening. 75 references among these were subject to secondary screening. As a result, because there were no Cochrane reviews, systematic reviews, randomized controlled trials, nonrandomized controlled trials, interventional studies, or observational research, and all of were case reports or case series, no references were adopted for evaluation of the body of evidence. For this reason, a qualitative review was conducted based on 19 case series and one group meeting report (Health and Labour Sciences Research Grant).

### 【Results of qualitative review】

From the above references, the five items of ① defecation disorders, ② dysuria, ③ movement disorders of the lower limbs, ④ sexual dysfunction, and ⑤ dysmorphic wounds were considered to be major long-term complications (sequelae).

### 【① Defecation disorders ② Dysuria】

Defecation disorders and dysuria are common long-term complications (sequelae) in many patients after surgery for sacrococcygeal teratomas. Defecation disorders may exhibit various symptoms such as soiling and constipation, while uropathy may exhibit urinary retention, hydronephrosis, urinary incontinence, vesicoureteral reflux (VUR), neurogenic bladder, nocturnal enuresis, urinary tract infections. Nationwide statistics on sacrococcygeal teratomas prenatally diagnosed in Japan indicated that defecation disorders or dysuria were observed in 8/72 (11%). According to Shalaby et al., soiling was present in 12/31 cases (39%), constipation in 6/31 cases (19%), and 58% of patients had no defecation disorders, with no correlation observed with gender, age at operation, pathological tissues, Altman classification, and the presence or absence of recurrence <sup>1)</sup>. In addition, they reported that urinary tract symptoms were found in 55% of patients. According to Derikx et al., there was no significant difference in terms of complete or incomplete resection, tissue type, volume, age, Altman classification, and gender, in both involuntary bowel movements and dysuria <sup>2)</sup>.

On the other hand, according to Partridge et al., sequelae of the urinary organs and anorectal was observed in 19/42 cases (45.2%), with risk factors including obstruction of the urinary tract and intestinal tract upon prenatal treatment intervention or prenatal imaging diagnosis, tumor recurrence, types other than Altman type I<sup>3)</sup>. Regarding the investigation on procedures, according to Barakat et al., 15 patients with Altman type I and type II undergoing sacroperineal resection did not have urinary disorders/defecation disorders, while 5/7 patients (71%) with Altman type III and type IV undergoing abdominosacroperineal resection had dysuria, soiling and constipation<sup>4)</sup>. However, while there are many reports on defecation disorders/dysuria, according to Cozzi et al., in a comparison of defecation and bladder functions between 13 adult patients with sacrococcygeal teratomas and a control group including 65 subjects with matching age and genders, there was no significant difference in defecation disorders/dysuria (SCT group 54% vs control group 38%)<sup>5)</sup>.

Based on the above reports, after sacrococcygeal teratoma surgery, patients may suffer from defecation disorders/dysuria, indicating the importance of conducting follow-ups taking these facts into consideration.

### 【③ Movement disorders of the lower limbs】

Movement disorders of the lower limbs have been reported in various studies: 1 of 20 cases (5.0%) by Lee et al.<sup>6)</sup>, 2 of 26 cases (7.7%) by Rintala et al.<sup>7)</sup>, 2 of 27 cases (7.4%) by Malone et al.<sup>8)</sup>, and 8 of 72 cases were also found in the nationwide statistics on sacrococcygeal teratomas prenatally diagnosed in Japan<sup>11)</sup> (11.1%). However, there was little description on the extent of the disorders. Malone et al. reported that two patients who had movement disorders of the lower limbs were able to walk, but both cases suffered extensions of the Achilles tendon. On the other hand, Zaccara et al.<sup>9)</sup> compared 13 cases after surgery for sacrococcygeal teratomas with a control group, reporting that there was no difference in walking speed and stride; however, when walking, the timing from when the toes leave the floor was earlier, with a significant decrease in the movement to extend the hip joint, a decrease in the movement of the ankle joint, a decrease in the muscular strength of the knee joint, and an increase in the muscular strength of the ankle joint, but no differences found in factors such as the extent of these differences and tumor sizes.

### [④ Sexual dysfunction]

There are few documents on sexual function. Concerning trouble during sexual intercourse, a study of 27 cases (average age 16.7) reported females who were incapable of sexual intercourse due to pain or males with impotence<sup>10)</sup>, while another study including 26 cases (average age 30.5, 6 males, 20 females) reported one male had impotence (20%) and two females (10%) experienced urinary incontinence during sexual intercourse<sup>7)</sup>. Regarding pregnancy/childbirth, in the same document, 10 of 26 patients had children on their own. According to a report on the Scottish national cohort by Shalaby et al.<sup>1)</sup>, 2 of 9 women over 16 years of age underwent pregnancy and childbirth, including one case of emergency caesarean section due to coiling of the umbilical cord and one case of vaginal delivery.

### 【⑤ Dysmorphic wounds】

According to Derikx et al., 31 of 77 patients (40.3%) thought that surgical wounds were unacceptable, with a significant difference between patients diagnosed prior to their eighth birthday and those with a large tumor (OR, 4.73; CL, 1.21-18.47;  $p = 026$ ), and those diagnosed over the age of one (OR, 0.19; CL, 0.04 - 0.98;  $p=048$ )<sup>2)</sup>.