

International Journal of Radiology and Diagnostic Imaging



E-ISSN: 2664-4444
P-ISSN: 2664-4436
www.radiologypaper.com
IJRDI 2023; 6(1): 39-45
Received: 11-10-2022
Accepted: 15-11-2022

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The prognosis of type 3 congenital pulmonary airway malformations may not be poor: Antenatal sonographic evaluation and postnatal outcomes of non-cardiac thoracic malformations in a large cohort

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DOI: <http://dx.doi.org/10.33545/26644436.2023.v6.i1a.304>

Abstract

Background: To analyze the prenatal sonographic findings, prevalence, and outcomes of non-cardiac thoracic malformations (NCTMs).

Method: This study included a retrospective analysis of electronic health records from February 2014 to March 2021. The follow-up sonographic examinations of the fetuses with diagnoses of NCTM and postnatal clinical follow-up were retrieved from electronically stored files and reports.

Results: Out of 19,640 fetuses, 25 fetuses were found to have NCTM with a prevalence of 0.12%. The most common NCTM was congenital pulmonary airway malformation (CPAM) (n=8, 32%), followed by pleural effusion (PE), pulmonary hypoplasia (PH), and congenital diaphragmatic hernia (CDH) (4 cases each, 16%), bronchopulmonary sequestration (BPS) (n=3, 12%), congenital lymphangioma (CL), and pectus excavatum (PEX) (1 case each, 4%). All type 3 CPAM cases and BPS cases resolved spontaneously *in utero*, whereas all type 2 CPAM (n=2) cases required surgery in the neonatal period and one of the type 1 cases resulted in fetal hydrops. All PE, PEX, and PH cases, and 25% of the CDH cases (n=1) were associated with underlying abnormalities. All cases with PH (n=4), all PE cases associated with hydrops (n=2, 50%) resulted in exitus *in utero*.

Conclusion: NCTMs are rare congenital anomalies with a prevalence of 0.12%. The most common type of NCTM was found as CPAM. All cases of type 3 CPAM and BPS showed spontaneous resolution *in utero*. The prognosis of type 3 CPAM may be favorable.

Keywords: Anomaly, fetal, malformation, non-cardiac, thorax

Introduction

Non-cardiac thoracic malformations (NCTMs) include a wide spectrum of lesions that arise in the embryogenic period and have potential effects on pulmonary development and function [1-3]. The most common NCTMs are congenital pulmonary airway malformation (CPAM), bronchopulmonary sequestration (BPS), congenital diaphragmatic hernia (CDH), and congenital lobar emphysema; less common lesions are mediastinal teratomas, lymphangiomas, bronchopulmonary foregut cysts, and pulmonary hypoplasia (PH) [1, 2]. These lesions consisting of lung, mediastinum, and thorax malformations, may have adverse effects on the pulmonary system [1, 2]. The anatomic location, size, and mass effect of the lesion determine the postnatal prognosis of the affected babies [2, 4]. Although some lesions regress or disappear *in utero*, some persist until the postnatal period [5]. Severe fetal morbidities including pulmonary hypoplasia, cardiac failure, polyhydramnios, hydrops, and perinatal death may occur [1, 2, 4, 5]. Depending on the antenatal diagnosis of congenital thoracic lesions, management options range from *in utero* therapy to termination of pregnancy [6].

The detection rate is reported as 1/10,000-1/35,000 pregnancies [1]. An increase in prenatal screening studies has led to diagnosing NCTM in routine screening at 18-20 weeks of gestation [1]. The detail of lesions can be defined as solid, cystic, or together with the presence of an aberrant vessel on account of the continued improvement in fetal imaging modalities, experience, the widespread availability of ultrasound, and better scanning devices [1, 7, 8]. Accurate diagnosis of these lesions is important for prognosis and management [6, 7, 9].

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Early prenatal detection of these lesions and accurate diagnosis is of crucial importance because NCTM can be associated with severe morbidities and mortality [6, 8, 9]. In this study, we aimed to investigate the antenatal sonographic findings, management, and outcomes of NCTM.

Materials and Methods

This retrospective cohort study was conducted at a secondary referral center specialized in maternal health care. Participants were selected from a cohort of 19,640 pregnant women who were referred for an obstetric ultrasound examination regardless of their trimester from February 2014 to March 2021. Electronic health records and the electronically stored radiologic images were retrospectively analyzed. Fetuses who were diagnosed as having thoracic malformations including cystic/solid thoracic masses, thoracic fluid collections, chest-wall deformities, and hypoplasia of the lung were included in the analysis. Fetuses with isolated cardiac anomalies/pericardial effusion were excluded from the study. All sonographic examinations were performed by a single experienced radiologist (first author of this paper) who was an expert in obstetric ultrasound examinations, using a high-resolution ultrasound device with a convex 6-1.9-MHz probe (Toshiba Aplio 500, Japan). The same machine was used throughout the study. In the identification of NCTM cases, the ultrasound examination details were documented in the written report and digital images, and these were electronically recorded along with other abnormal findings of the fetuses as a local protocol. The NCTMs were divided into seven subgroups according to sonographic findings. These seven subgroups included CPAM, pleural effusion (PE), PH, CDH, BPS, congenital lymphangioma (CL), and pectus excavatum (PEX). Sonographic features such as solid/cystic thorax masses, vascularity of the lesions, pleural effusion, and pulmonary hypoplasia were recorded and used for the differential diagnosis of NCTM. Regarding cystic masses, a single dominant cyst (>10 cm) or several large cysts (2-10 cm) were classified as type 1 CPAM, multiple small cysts (<2 cm) were classified as type 2, and multiple small cysts with a solid appearance on sonography were classified as type 3 CPAM [10]. Fetuses who were suspected of having pulmonary hypoplasia without an intrathoracic mass were evaluated using the formula of the fetal thoracic/abdominal circumference (TC: AC) ratio in the axial plane at the level of the four-chamber view of the heart. The TC: AC ratio <0.6 was used to predict pulmonary hypoplasia [11]. Fetuses with NCTM were followed every 2-3 weeks until birth through sonographic examinations as a local protocol and any lesion regression or progression were recorded. Postnatal follow-up included postnatal sonography and pediatric examination of the infant. Clinical data about babies with NCTM were retrieved from the electronic health records of the pediatric clinic of the study centre. The demographic data of the patients including the mean gestational age at the time of diagnosis, the sex of the fetuses, associated anomalies, and clinical outcomes of fetuses with NCTM were retrieved from health records. The research was conducted ethically in accordance with the guidelines for human studies and World Medical Association Declaration of Helsinki. The study was approved by the local research ethics committee (No: 21/173). Statistical evaluations were performed using the Statistical

Package for the Social Sciences package (SPSS 22.0). The normality assumption of the variables was checked using the Shapiro-Wilk test. Descriptive statistics were used as mean, standard deviation (SD), median, number, and frequency.

Results

The final analysis included 25 fetuses (0.12%) who were diagnosed as having NCTM out of 19,640 fetuses. All fetuses had complete postnatal pediatric records. The mean \pm SD gestational age of fetuses at the time of diagnosis was 18.4 ± 2.7 weeks of gestation and ranged between 11 to 25 weeks. The most commonly diagnosed types of NCTM according to their sonographic findings were CPAM (n=8, 32%), followed by pleural effusion (PE) (n=4, 16%), pulmonary hypoplasia (PH) (n=4, 16%), CDH (n=4, 16%), BPS (n=3, 12%), congenital lymphangioma (CL) (n=1, 4%), and pectus excavatum (PEX) (n=1, 4%) (Figure 1). Type 1, type 2, and type 3 CPAM were observed in two (25%), two (25%), and four (50%) cases out of eight cases, respectively (Figures 2-4).

The clinical features of NCTM are presented in Table 1. The fetal anomalies accompanying NCTM and outcomes of fetuses are summarized in Table 2.

Of the eight CPAM cases, 62.5% (n=5) were asymptomatic, and 25% (n=2) of them underwent elective lobectomy in the neonatal period due to respiratory compromise. One underwent termination of pregnancy due to developing anhydramnios and hydrops at the 20th week of gestation. All type 3 CPAM cases (n = 4) showed spontaneous regression *in utero* and remained asymptomatic in the neonatal period. The outcomes of the CPAM subtypes are summarized in Table 2.

One of the fetuses diagnosed as having CDH died following labor, one underwent termination of pregnancy due to maternal request, and two underwent surgery in the neonatal period (Figure 5-7). One fetus who underwent surgery was successfully cured and was followed uneventfully until two years of age. The other fetus died soon after surgery due to respiratory compromise. Liver herniation accompanied in this case and the lung-to-head circumference ratio (LHR) of this case was measured as 0.4 at the 33rd week of gestation (Figure 7d).

Two fetuses with PE as a component of fetal hydrops were exitus *in utero* (Figure 8). All BPS cases showed spontaneous regression *in utero* (Figure 9). All of the fetuses with PH was exitus *in utero* or after birth. The fetus with lymphangioma was cured with bleomycin therapy (Figure 10).

Discussion

In this study, the prevalence of NCTM was found as 0.12% and the most common type of NCTM was CPAM with a prevalence of 0.04%. All fetuses with type 3 CPAM and BPS regressed spontaneously *in utero*, while other types of NCTM were majorly presented with adverse outcomes.

NCTMs are a heterogeneous group of thoracic anomalies that vary greatly in their presentation, rates, risk of morbidity, and mortality [12]. Although the underlying mechanism is not fully understood, any inhibition of lung development in the embryogenic period by infections, vascular interruption or obstruction might be responsible for NCTMs [12]. In the literature, 30-40% of congenital lung anomalies are reported as CPAM [13]. CPAMs are usually

diagnosed at the gestational age of 18-21 weeks. The characteristic sonographic findings of CPAM are cystic lesions of variable sizes or uniformly echogenic lesions on one side of the lung [5]. CPAM cases accounted for 3.2% of all NCTM cases with a mean gestational age of 17.7 weeks in the present study. Type 3 cases were diagnosed more frequently than type 1 and type 2 cases in this cohort. Gross *et al.* proposed that type 1, type 2, and type 3 cases were found in 70%, 15-20%, and 10% of cases, respectively [14]. In the literature, type 1 lesions were suggested to have the best prognosis, whereas type 3 lesions were proposed to have the worst prognosis [15, 16]. On the other hand, babies with non-hydropic, particularly smaller type 3 lesions, have a 97% survival rate [10]. In the current study, half of type 1 CPAM cases required termination *in utero* and all type 2 CPAM cases required surgical intervention. By contrast, all fetuses with type 3 resolved spontaneously *in utero*. The underlying causes of spontaneous regression in the type 3 cases is still unknown [17]. It was hypothesized that an asynchrony in the embryologic development of the lung, leading to proliferation of the cells or apoptosis, might result in CPAM, and therefore, an obstructing mucous plug in the bronchus might induce transient tissue growth and mimic a microcystic CPAM lesion until the obstruction resolves [18]. However, we could not conclude from our data that transient non-CPAM findings including obstructing mucous plugs lead to misdiagnosis of Type 3 CPAM regression. Instead, the criteria for prenatal ultrasonographic diagnosis needs to be reevaluated and the lesions that do not regress may play an important role in the diagnosis of CPAMs.

The worse prognosis of type 1 and type 2 cases in our study might be explained by the hypothesis based on the fact that cysts may expand more rapidly and become larger than solid lesions in the thorax [17]. Histopathologic classification may have limited value for prognosis; lesion size is the main determinant of perinatal survival. Even the size of the mass is more discriminating for prognosis than the pathologic nomenclature of the lesion (e.g., CPAM vs. BPS) [17]. Survival is expected to be 100% in fetuses with small lesions and without mediastinal shift or hydrops [2, 17]. The treatment of hydrops in association with a cystic type 1 or 2 CPAM is *in utero* shunting [8].

The characteristic appearance of BPS on antenatal ultrasound is a triangular-shaped, echogenic solid mass. A few distinctive features of BPS such as demonstration of a branch from the systemic vascular circulation may be helpful for the differentiation of BPS from other NCTM types [19]. Nevertheless, around 12-16% of BPS lesions could be misdiagnosed, especially type 3 CPAM [20, 21]. The prognosis of BPS mostly depends on the mass effect and development of hydrops, as in CPAM [22]. All BPS cases in this study appeared to resolve *in utero* and no complications occurred in the neonatal period.

The types of CDH are illustrated in Figure 6. CDH frequently appears on the left hemithorax; all CDH cases in our study were located on the left side (Figure 7). The prognostic factors of CDH were reported as follows: liver herniation into the chest, early gestational age at the time of diagnosis, large diaphragmatic defect, and the presence of associated major anomalies [23, 24]. The LHR is useful for estimating the contralateral lung area for patients at risk of PH development. A value less than 0.9 is associated with a worse prognosis, whereas higher than 1.4 is associated with a better prognosis [24, 25]. The LHR value of our CDH case

with liver herniation was 0.4 at the 33rd gestational week indicating a worse prognosis (Figure 7d). The baby died soon after surgery on the second day of life.

In the present study, all PE cases were bilateral and symmetric indicating hydrothorax. Hydrothorax may be found primarily or as a part of fetal hydrops [9]. With the development of hydrops, high mortality rates were reported [9]. Similar to the literature, two out of four PE cases in this study presented with hydrops and both died *in utero*.

PH is frequently related to an underlying abnormality such as oligohydramnios, thoracic mass, skeletal dysplasia or a renal anomaly that causes poor renal function [8, 26-28]. In this study, all cases with PH were died during the antenatal or postnatal period and presented with accompanying fetal anomalies or adverse outcomes including achondrogenesis, thanatophoric dysplasia, bilateral multicystic dysplastic kidney, and anhydramnios. The TC or TC: AC ratio can be used for the prediction of PH except for accompanying intrathoracic mass [29]. In the case of intrathoracic masses, the thoracic circumference can be measured as normal [29].

CL also called cystic hygroma, is an uncommon malformation of the lymphatic system. A large proportion of fetuses with CL have chromosomal or structural anomalies [30]. As a very rare presentation, we diagnosed a thin-septated, non-infiltrative CL located on the thorax with a normal karyotype. The baby was treated with bleomycin, a chemotherapeutic agent, and the prognosis was favorable because cure was achieved. Our results were similar to the findings of Lu *et al.* who showed that prognosis was independent of the lesion size or the presence of septa [31]. The main prognostic factor of CL is associated with the presence/absence of infiltration to surrounding structures [32].

PEX, depression of the lower part of the manubrium, is a usually sporadic disorder but may be associated with Marfan syndrome, Ehlers-Danlos syndrome, Noonan syndrome, and trisomy 21 [32]. Only two cases with a prenatal diagnosis of PEX have been reported to date, one isolated case and one case with trisomy 21 [32, 33]. The prognosis depends on the severity of the chest malformation and cardiopulmonary functions in PEX cases [33]. Our case was non-isolated and the prognosis was favorable because the chest malformation was mild.

The major limitation of the current study was the lack of a histopathologic diagnosis of the cases. None of the BPS cases and type 3 CPAM cases were diagnosed histopathologically; therefore, possible misdiagnoses could not be excluded. Postnatal imaging only included postnatal ultrasound findings. Magnetic Resonance Imaging may have been better particularly for showing *in utero* regression in small lesions. Another limitation of the study was its retrospective nature and the relatively small sample size. The generalizability of the findings regarding the prevalence and outcomes presented in this study should be approached cautiously. However, the reported data are clinically relevant owing to the dearth of evidence in the literature owing to its rarity. The major strength of this study was that all cases were evaluated by a single experienced sonographer, which eliminates inter-observer variability.

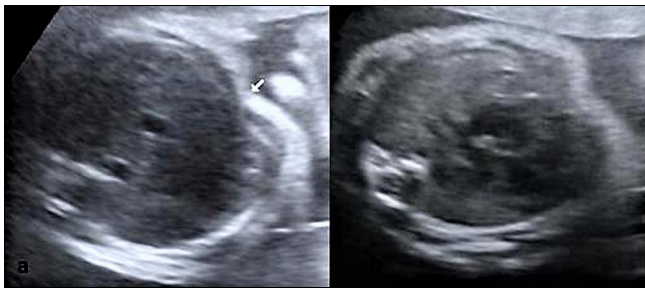


Fig 1: a. and b. Pectus excavatum. The depression of the manubrium sterni is demonstrated on the axial section of the thorax



Fig 4: Type 3 congenital pulmonary airway malformation a. The axial view of the thorax. An echogenic mass in the right side of the lung. b. No visible vascularisation of the mass on doppler sonography. c. The saggital view of the thorax revealing supradiaphragmatic echogenic mass



Fig 2: Type 1 congenital pulmonary airway malformation. A dominant cyst in the right lung in a fetus of 19 weeks of gestation

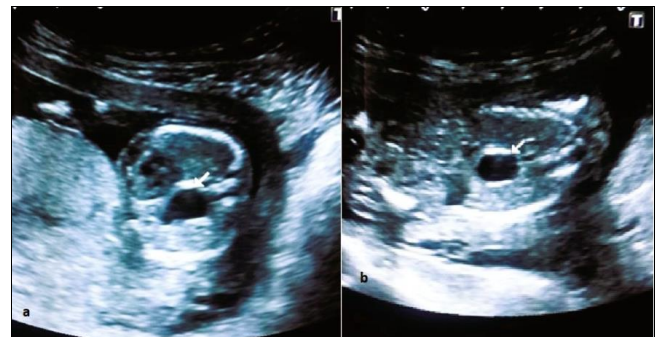


Fig 5: CDH a. and b. The axial and saggital views of the thorax. Left sided CDH in a fetus of 17 weeks of gestation. The stomach was detected in the left hemithorax



Fig 3: Type 2 congenital pulmonary airway malformation. Multiple cysts (<2 cm) in the right lung in a fetus of 20 weeks of gestation

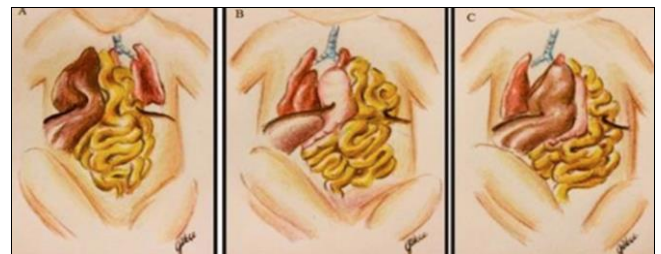


Fig 6: Illustration of the types of congenital diaphragmatic hernia (CDH) a. Right-sided CDH. Herniation of the liver and the intestinal segments through the right hemithorax. b. Left-sided CDH without liver herniation (Liver-down CDH) c. Left-sided CDH with liver herniation (Liver-up CDH)

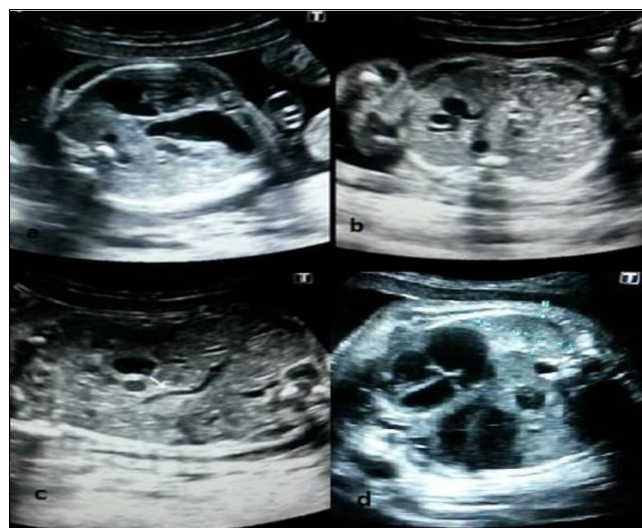


Fig 7: Congenital diaphragmatic hernia (CDH) a. and b. Left-sided CDH with liver herniation in a fetus of 24 weeks of gestation. Note the deviation of the heart to the right side. c. The saggital image demonstrates the liver herniation. d. The measurement of the contralateral lung area to calculate the lung/head ratio in the same fetus at the 33th gestational week



Fig 8: Pleural effusion (PE) as a component of hydrops fetalis a. Bilateral PE in the axial thorax view. b. The parasagittal view of the abdomen and the thorax showing the PE and the ascite in abdomen. c. The axial view of the cranium demonstrating the edema of the scalp as a component of hydrops fetalis



Fig 9: Bronchopulmonary sequestration a. and b. An echogenic, triangular-shaped mass on the base of the left hemithorax



Fig 10: The congenital lymphangioma is located on the right side of the thoracic wall

Table 1: Clinical features of the non-cardiac thoracic malformations

Non-cardiac thoracic malformations (n=25)	Gestational age at diagnosis (week) (median ± IQR) (min-max)	Side of the lesion	Gender of the fetuses
Congenital pulmonary airway malformation (n=8)	17.5±2.75 (15-20)	4 left, 4 right	3 female, 5 male
Pleural effusion (n=4)	19.5±2.5 (18-21)	3 bilateral	2 female, 2 male
Pulmonary hypoplasia (n=4)	18.5±1.75 (18-20)	4 bilateral	1 female, 3 male
Congenital diaphragmatic hernia (n=4)	17±0 (11-24)	4 left	2 female, 2 male
Bronchopulmonary sequestration (n=3)	18±0 (18-19)	3 left	1 female, 2 male
Congenital lymphangioma (n=1)	25±0	Right	Female
Pectus excavatum (n=1)	19±0	Median	Male
Total (n=25)	19±0 (15-20)	11 left, 5 right, 7 bilateral, 1 median	10 female, 15 male

IQR: Interquartile range

Table 2: Outcomes of non-cardiac thoracic malformations with associated anomalies and co-morbidities

Non-cardiac thoracic malformations (n=25)	Type of cases	Number of cases	Outcomes	Associated anomalies and co-morbidities
Congenital pulmonary airway malformation (n=8)	Type 1 (n=2)	1	Termination at the 20th gestational week	Hydrops, anhydramnios
		1	Unremarkable in neonatal period /Asymptomatic	Hydrops, anhydramnios
	Type 2 (n=2)	2	Successful neonatal surgery at the 6th months of life, followed until 2 years of age	
Pleural effusion (n=4)	Type 3 (n=4)	4	<i>In utero</i> regression at the third trimester/Asymptomatic	
		2	Intrauterine exitus	Hydrops
		1	Survived (3 months follow-up)	Parvovirus
		1	Survived (6 months follow-up)	Trisomy 21
		1	Exitus soon after birth	Achondrogenesis
Pulmonary hypoplasia (n=4)		1	Exitus soon after birth	Thanatophoric dysplasia
		1	Intrauterine exitus	Anhydramnios
		1	Postnatal exitus at the 3rd day of life	Bilateral multicystic dysplastic kidney
Congenital diaphragmatic hernia (n=4)		1	Postnatal exitus at the first week of life	Ventricular septal defect
		1	Surgery within 24 hours of life, followed until 2 years of age	
Bronchopulmonary sequestration (n=3)		1	Exitus after surgery at the second day of life	
		1	Termination of pregnancy at the 16 th gestational week	
		3	Regression (at the 30 th , 33 rd , 36 th gestational weeks)	
Congenital lymphangioma (n=1)		1	Cured with Bleomycin therapy at the 6th month of life	
Pectus excavatum (n=1)		1	No cardiopulmonary complication	Mild ventriculomegaly

				Perimembranous ventricular septal defect Hypospadias
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Conclusion

NCTMs are rare congenital anomalies with a prevalence of 0.12%. The most common type of NCTM was found as CPAM and all type 3 CPAM cases and BPS cases showed spontaneous resolution *in utero*. The prognosis of type 3 CPAM may be favorable. The antenatal diagnosis of these anomalies may have a crucial role for appropriate counseling and management with good timing.

Acknowledgments

Authors wish to thank Specialist Murat Yassa MD for his sincere support and supervision in this manuscript.

Conflict of interests

The authors declare they have no potential conflict of interest regarding the investigation, authorship, and/or publication of this article.

Funding

This study received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

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How to Cite This Article

Gokce ANNAC, AB TEKIN. The prognosis of type 3 congenital pulmonary airway malformations may not be poor: Antenatal sonographic evaluation and postnatal outcomes of non-cardiac thoracic malformations in a large cohort. International Journal of Radiology and Diagnostic Imaging. 2023;6(1):39-45.

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