CLINICOPATHOLOGICAL STUDY OF CRYPTOCHID TESTIS

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CERTIFICATE

Certified that the dissertation entitled "CLINICOPATHOLOGICAL STUDY OF CRYPTORCHID TESTIS' is the original work undertaken by Dr. R. ARUNKUMAR under our guidance and supervision, in the Department of Paediatric Surgery, Institute of Child Health and Hospital for Children, Madras Medical College, Chennai-3, during the period of his post graduation in M.Ch. Paediatric Surgery from 2005-2008, in partial fulfillment of the university rules and regulations for the award of M.Ch. degree.

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DECLARATION

I declare that this dissertation entitled “CLINICOPATHOLOGICAL STUDY OF CRYPTORCHID TESTIS” has been conducted by me at the Institute of Child Health and Hospital for Children. It is submitted in part of fulfillment of the award of the degree of M.Ch (Pediatric Surgery) for the August 2008 examination to be held under the Tamil Nadu Dr. M.G.R. Medical University, Chennai. This has not been submitted previously by me for the award of any degree or diploma from any other university.

Dr. ARUNKUMAR
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HISTORICAL PERSPECTIVE

The importance of a descended testis has been known since ancient times, but the mechanism of descent remained obscure until 1786, when HUNTER dissected the human fetus and found the intraabdominal testes connected to the inguinoabdominal wall by a ligament called gubernaculum appearing to guide the testes to the scrotum.

Although cryptorchidism has been studied intensively both experimentally and clinically during the past century, the cause of the condition remains poorly understood. Moreover, despite surgical advances in the technique of orchiopexy, the individual management options, especially for non-palpable testis remains controversial.

The clinical issues related to the etiology, diagnosis, histopathological changes and the management of cryptorchidism are
the focus of attention during the current decade as it has a profound bearing on the future fertility potential of the individual.

**INTRODUCTION**

Cryptorchidism contributes the most common genital problem, and one of the most common overall problem encountered in pediatric surgical practice. Cryptorchidism literally means ‘*hidden testis*’. The term is derived from greek word ‘Kryptos’ and ‘Orchis’ meaning ‘*hidden*’ and ‘*testis*’ respectively, and refers to the absence of testis from the scrotum.

Although some interchangeably call a testis ‘*cryptorchid*’ or ‘*undescended*’, the terms are not synonymous, because cryptorchid testis may also be ‘*ectopic*’, or ‘*absent*’, while undescended testis typically testifies a testis which is arrested anywhere in the normal course of its descent from the intraabdominal position to the scrotal position.
Normal and abnormal testicular descent

Testicular and epididymal descent is believed to be necessary for most mammals and man to produce a fertile ejaculate; the 2-3 degrees cooler temperature provided by the scrotum appears crucial in this regard.

The process of testicular descent can be divided into 3 phases:

1) **Transabdominal migration (8-15 Weeks)**

The cranial suspensory ligament regresses under the influence of androgen testosterone, and the gubernaculum proliferates and swells to guide the testis further down. The result of transabdominal migration in humans is testicular position at the internal inguinal by the 12th week of gestation.

2) **Process Vaginalis: (15-24 Weeks)**
During the 3rd month of gestation the processus vaginalis grows along the gubernaculum and extends from the peritoneum into the inguinal canal and scrotum bringing with it the testis further down. The testis does not change position between 3 and 7 months of fetal life.

3) **Transinguinal descent (24-28 weeks)**

This occurs very rapidly. The testosterone acts on the **genitofermoral nerve** causing the release of **Calcitonin gene related peptide (CGRP)**, causing the regression of gubernaculum and the migration of the testes to the scrotum. Normally the processus vaginalis closes completely before birth, but when the testis is undescend, the processus vaginalis remains patent.
**Definition and Classification:**

Several existing definitions and classifications attempt to communicate the physical findings related to cryptorchidism. Clearly the two most significant categories include:

- **Palpable**: 80%
- **Non Palpable**: 20%

**Palpable**:
- True undescended testis: 75%
- Ectopic testis: 5%

**Non Palpable**: 
Intrabdominal : 60%
Inguinal : 20%
Absent testis : 30%

**Incidence:**

- Premature : 33%
- Full term : 3%
- 1 year : 0.8 – 1%

Unilateral : 68%
Bilateral : 32%

Right Side : 70%
Left Side : 30%

**RETRACTILE TESTIS:**

These are often misdiagnosed as undescended testis, and will not be entertained in this category. The retractile testis can generally be manipulated into scrotum, where it will remain momentarily until restimulation results in retraction into the groin due to a cremasteric reflex. Differentiation of the retractile from the true undescended testis is not always easy, and the diagnosis of a retractile testis is occasionally made on a examination under anesthesia.
ECTOPIC TESTIS:

This is a normally developed testis with only an abnormal migration. These are not in actual terms included under the term Undescended testes. The most common site of ectopia is the superficial inguinal pouch of Denis Browne. They are also found in positions like femoral, pubic, penopubic, and perineal positions.

VARIOUS TESTICULAR LOCATIONS

ETIOLOGY:

1. Pituitary – gonadotropin deficiency
2. Primary Testicular abnormality

3. Anatomical abnormalities

4. Dysgenetic testes/Regression syndrome

This study is done to find out the histological changes in cases of UNDESCENDED TESTIS to give a prognostication of future fertility and the risk of developing future malignancy in the form of ‘intratubular germ cell neoplasia’.

**LITERATURE REVIEW**

An understanding of normal testicular development is helpful to the diagnosis and management of cryptorchidism. Normal male phenotype is the result of a cascade of gene activations and hormone-receptor interactions that are tightly regulated temporally and spatially in the embryo.

**Embryogenesis:**
This begins in the 5th week of gestation, when proliferation of coelomic epithelium and the underlying mesenchyme medial to mesonephros produces the bipotential gonad. Formation of this bipotential gonad is dependent on such genes as the Wilm’s Tumour gene (WT-1) and Steroidogenic factor (SF-I).

Epithelial primary sex cords then grow into the underlying mesenchyme, resulting in the development of a cortex and medulla. The fate of the bipotential gonad is determined by the presence or absence of a normal SRY (Sex determining Region-Y linked) gene situated in the short arm of Y chromosome.

Under the activation of SRY and other downstream testis determining genes, the cortex regresses and the medulla develops as testis, beginning in the 6th week of gestation. Primordial germ cells situated in the wall of the yolk sac from the 4th week of gestation migrate along the dorsal mesentry of the hindgut to reach the gonad by 6th week gestation. Sertoli cells appear by wk 6, and the Leydig cells appear by wk 8 to produce MULLERIAN INHIBITING SUBSTANCE and TESTOSTERONE respectively (Jirasek)(1).
Migration of the Germ Cells from the Yolk Sac to the Gonadal Ridge
Testicular Descent
To achieve the normal male phenotype, it requires normal hormonal and its receptor function, quantity, location and timing. Given these the Mullerian Inhibiting Substance causes involution of the ipsilateral mullerian duct and the testosterone promotes masculinization of the ipsilateral Wolffian duct to provide normal male internal and external genitalia by wk 10-13 of gestation.

Development of male external genitalia including the scrotum, occur between wk 10 and 15 of gestation, and results from the conversion of testosterone to dihydrotestosterone by the enzyme 5α reductase type 2 in these tissues.

Proper development of the scrotum is important because it enables the testis to migrate outside of the body and reside in an extracorporeal environment conducive for its growth.

**Postnatal development:**

After birth, continued changes occur in the various cell compartments of the testis. Initially the primordial germ cells differentiate into gonocytes, lying adjacent to the basement membrane,
and then into **fetal spermatogonia**, which remains postnatally and can be seen through the 7th year. Postnatally between the 3rd and 5th month after birth, they transform into **Type A spermatogonia**, then into **Type B spermatogonia** by 4 years of age, as normal steps in the maturation process.

The germ cell undergo a quiescent period until puberty, with the onset of spermatogenesis. At this time the spermatogonia transform into **Primary spermatocytes**, which duplicate their DNA content and then undergo meiotic division (transformation) into **Secondary spermatocytes**, with the haploid number of chromosomes.

**Spermatids** develop subsequently with the development of puberty, ultimately differentiating further into **Spermatozoa**. Puberty onset occurs in most boys by 13 years of age, and is completed in most by 15 years (Hadziselimovic, 1987)(2).

Simultaneous changes in **Leydig** cells are present at birth, and are observed through the first 4 months, when their number decreases and their transformation into ‘**juvenile**’ variety begins. No further changes
occur until puberty when it becomes ‘adult’ variety. The increase in number and histological activity are coordinated temporally with increase in testosterone secretion produced by them. Leydig cells, in addition to producing testosterone, also contain Aromatase, NO synthase, Substance P, as well as Methionine-enkephalin immuno reactivity.

Sertoli cell changes in developing testis are now more fully understood, and are seen lining the seminiferous tubules. At birth, they number 40±3-4 /tubule, and at puberty 10±1-2/tubule. Although their numbers per tubule decreases with aging, their size increases 8-10 times by puberty, concomitant with increase in tubular diameter. Histologically, sertoli cells can be distinguished into Sa, Sb and Sc (adult) in addition to Sf (fetal) forms as puberty progresses, as normal steps in the maturation process. The Sf variety is believed to secrete Mullerian Inhibiting Substance (JOST, 1970)\(^3\).

The functions of the sertoli cells have only recently been recognized and it is obvious that the sertoli cells are not a passive
structure. Junctions between sertoli cells are among the tightest in the body and divide the seminiferous tubule into an outer ‘basal’ compartment containing spermatogonia and pre-leptotene spermatocytes, and an inner ‘ad luminal’ compartment containing the more mature forms. Junctions develop at puberty and define the ‘blood testis’ barrier, which gives the ad luminal compartment a protective environment.

Human sertoli cells, in addition to producing MIS, also secrete ABP (androgen binding protein); Inhibin, which suppresses FSH secretion; and other substances like TGF-X; Transferrin; CPK; Testibumin; LDH; Alk PO4 and γGGT.

Aromatisation of testosterone to estradiol occurs in the sertoli cells under FSH control. Sertoli cells also have phagocytic action and spermatogenesis regulating capacity. Thus sertoli cells have important effects on differentiation, spermatogenesis and endocrine function.
Although earlier studies indicated that testicular development is static during the first years of life, stereologic studies showed progressive increase in testicular volume from birth to adulthood. This increase is not sufficient during the first 5-6 years to produce distinctive changes by light microscopic study.

In Muller and Shakkeback study (1978), mean tubular diameter was constant through year 5, with slight enlargement through year 14, and a significant increase in tubular diameter between 14-18 years old. The average mean tubular diameter is 80-90 microns.

The numeric density of germ cell nuclei per tubule increased progressively from age 5, as did the total number of germ cells. **Seminiferous tubules** occupied about half the testicular volume before puberty and about 67% from 14-18 years. By 8 years **primary spermatocytes** may be evident. Development becomes progressive thereafter. **Sertoli** cells become more mature with increased cytoplasm and oval, often nucleolated nuclei.
Spermatogenesis and spermiogenesis may be seen by year 11. Leydig cells, usually not evident histologically after 4 months, reappear as soon as 8 years and more numerous at 11 to 14 years.

After spermatogenesis has been completed, the testis resembles the adult testis. Changes related specifically to advancing age are not readily discernable in an individual testis.

After age 40 years, LH & FSH increase, and serum Testosterone values slowly decrease. Weights of the testes are similar in young and older men, but the percentage of total testicular weight represented by the tunica albugenia and the thickness of tunica albugenia are greater in older adults. The weight of the testicular parenchyma is similar or reduced in older, but the daily sperm production per testis and per gram of testis is greater in young men.

With increasing age there is reduced volume of parenchyma, seminiferous tubules, and seminiferous epithelium; in addition the number of sertoli cells are reduced per gram, per testis and per serminiferous tubule. Johnson and Kaber (1968) described reduced
number of **leydig** cells and **myoid** cells as age progresses. **Honore** (1967)\(^{(6)}\) however, indicated that there is **leydig cell hyperplasia**, but this was not assessed in a quantitative fashion. He also described tubular sclerosis, focal mononuclear cell infiltration, capsular smooth muscle hyperplasia, and dilation of rete testis. **Johnson** (1968)\(^{(5)}\) also described increased thickness of myoid cells, and extracellular compartment as age progresses, but no difference in volume density of myoid cells, and he interrupted the changes as secondary to reduction in tubular length.

In the humans, in general, **spermatogenic** and **hormonal** function do not abruptly cease. It is difficult to determine the causes of various changes, but decrease in hormonal function is probably at least partly due to loss of about 8 million **leydig** cells per decade.

Reduced function and altered structure of the testis as age progress have multiple etiologies, including arteriosclerosis, reduced nutrition and intercurrent disease.
Normal development of the Hypothalamic-Pituitary-Testicular axis.

During the 8th fetal week, the testes begins secreting testosterone under the stimulation of Maternal Chorionic Gonadotropin hormone, thereby influencing development of internal ducts and external genitalia, and perhaps testicular descent. Subsequent activation of fetal Hypothalamic-pituitary-testicular axis results in continual of gonadotropin stimulation of testosterone production (Smail Etal, 1981)(7)

At term, and during the first 6 months after birth, LH, FSH and Testosterone are elevated (Forest etal, 1973)(8), Thereafter all the three fall progressively, except for a small peak in LH activity noted between 4 and 6 years of age, paralleling the appearance of well developed ‘juvenile’ Leydig cells and primary spermatocyte (Waaler, 1979)(9)
Puberty onset marks the next notable event; with decreasing sensitivity of the **gonadostat**; increased **Gonadotropin Releasing Hormone** (GNRH) release and ‘**pulse synchronized**’ increase in LH and **testosterone**, and a lesser increase in **FSH**, (Boyar et al, 1974)(10) **leydig** cell numbers and activity increase, **sertoli** cells undergo completion of maturation and spermatogenesis also become fully complete. These events illustrate the synchronous interaction of the hormonal and cellular changes occurring at this time.

**Abnormal Hormonal findings:**

Characterization of hormonal profiles in **Cryptorchid** boys of varying ages has done much to aid our understanding of the condition. Some studies have identified abnormalities in **hypothalamic-pituitary-testicular** axis. These findings are the more revealing, and lend credence to the belief that this problem has a hormonal basis.

Normal boys with descended testes demonstrate a transient rise in testosterone levels, peaking at 60 days after birth. This physiololgic
occurrence has been described as a ‘**marking phenomenon**’, eventually allowing for normal function in male organs, possibly including spermatogenesis, later in life. In both unilaterally and bilaterally cryptorchid boys, a ‘**blunted**’ response occurs, and the **basal testosterone** levels are all lower than in normal boys (**Gundral et al., 1978**). In addition, a **blunted testosterone response** to HCG stimulation is observed in about one third of those children.

There is also a defective **LH** secretion present early in life in some **cryptorchid** children, suggesting that early delay in **LH** secretion may be responsible for the abnormal testosterone response at 60 days, and may relate to abnormal descent. As these findings are noted both in unilateral and bilateral **cryptorchids**, a primary decrease in **LH** secretion rather than a primary **leydig** cell defect appear to be the cause. Because it appears so early in life, an acquired **leydig** cell defect secondary to abnormal testicular position does not appear to be likely. Other studies involving large number of infants have failed to confirm these hormonal abnormalities, in part may be related, to the **heterogenous** nature of **cryptorchidism**.
Those with reduced LH levels, in general, have the lowest germ cell count (Hadziselinovic) (21). These reports indicate that in some patients, the early LH-testosterone defects persists throughout puberty. By puberty, testosterone response to HCG normalizes, and most cryptorchid boys undergo normal puberty. Mean FSH levels in cryptorchid children are usually normal.

Adults with bilateral cryptordism and late treated bilateral cryptorchidism are virtually always sterile, and may undergo premature androgen failure, ie in their mid 40’s (Amelar, 1966)(12) These observations indicate the progressive nature of this disease process.

**Histology and ductal development in cryptorchids:**

Histological appearance of cryptorchid testis is completely different from that of a normally descended testis. Whereas the later undergoes age dependent, progressive development the undescended testis is constantly retarded.
Cryptorchid testis in the adults are uniformly devoid of germ cells as age progresses. Their tubular diameter is usually diminished, and their basement membrane are thickened. and sometimes hyalinized. Sertoli cells are prominent often appearing as a ‘Sertoli cell only’ picture. The leydig cells appear relatively hyperplastic, and marked interstitial fibrosis often occurs.

These changes are already evident at puberty, the most obvious being related to the onset of spermatogenesis. Germ cells at this time normally develop the capacity to progress through a series of mitotic divisions (Spermatogonia), meiotic divisions (Type A and Type B spermatocytes, morphologic transformation from round to elongated forms (Spermatoids), and finally release Spermatozoa into the tubular lumen.

Prior to these events, the germ cells in the prepubertal testes are of the prespermatogonial type. Distinction between prespermatogonia and spermatogonia is important because only with
spermatogonial formation can the process of spermatogenesis be initiated.

Cryptorchid testis at puberty are variable in appearance, but definitely demonstrate abnormalities of germ cell morphology and number. Spermatogenesis is uncommon, with the exception in the more distally situated testis, and appear arrested in the prespermatogonial and spermatogonial level (Gondas et al, 1982)(13). Germ cells numbers remain diminished. Leydig cells are usually reduced in number and appear atrophic when examined by electron microscope and volumetric analysis. Despite these observation testosterone production is adequate to initiate and maintain normal puberty in most cases, even in bilateral cryptorchid individuals, attesting to the functional capability of these Leydig cells at this age, regardless of their appearance (Duckerman et al 1979).

Histological analysis of cryptorchid testes before puberty has provided the most insight and benefit in understanding their effect on fertility. These observation, in particular, have resulted in a dramatic alteration in the recommended age at orchiopexy. In an article in the
International Journal of Urology 2007, Park KH et al made a study to determine the optimal timing for orchiopexy and concluded that to protect future fertility potential orchipexy be performed no later than 2 years of age in patients with palpable inguinal testis.

As early as 1929, it was noted that the younger the age an undescended testis is examined, the more closely it resembles the histologic appearance of the descended testis (Cooper 1929)(16). Within the first months of life, the number of germ cells in cryptorchid testis and descended testis is equal, but by the end of the first year, however differences already exist. Although, the mean number of germ cells in both is equal, a wide standard deviation exists among cryptorchid testis, implying that same already have diminished germ cells (Mengel etal 1974)(17). The number of spermatogonia does not increase as in descended testes, although the total number of germ cells remain normal (Hadziselimoric)(17) Failure of gonocyte transformation has been implicated, paralleling a reduction in leydig cell number.
The scrotal testis in an **unilateral cryptorchidism** has as a rule, more germ cells than **cryptorchid** one, but fewer than age matched descended testis.

In upto 40% of **unilateral cryptorchid** boys, the combined germ cell count of both testes do not exceed that for **bilateral cryptorchidism**, indicating a deficiency in both testes, and some of those testes are already devoid of all germ cells as early as the first year of life ([Hedinger 1979](#18)). In general, the reduction in germ cells in the descended testes is directly proportional to the severity of reduction in the **cryptorchid** one. This provides the basis for Testicular dysgenesis/Regression syndrome.

In addition to **age** and **gonadotropin** level as the significant factors correlating directly with **histologic** abnormalities in **cryptorchidism**, there is a direct relation between testes **location** and **germ cell count**.

Although **intraabdominal** testis within the first year have a normal number of germ cell number, 90% demonstrate complete loss of germ cell by puberty. Only 41% of **inguinal** and 20% of **penoscrotal** testes undergo similar loss ([Hadziselimovic](#)). Structural abnormalities
of the **ductal** system associated with **cryptorchidism** also occur more frequently in higher **undescended** testis. Grossly identifiable lesions of the **vas deferens** and **epididymis** occur clinically in atleast 1/3 of **undescended** testes, especially in an **intraabdominal** position. These are characterized by various degrees of detachment between the **epididymis** and **testis** and by elongation and looping of the caudal **epididymis** and **vas**. An elongated or extended **epididymis** is the most commonly encountered **ductal** abnormality associated with **cryptorchid** one.

Whereas gross detachment may be clinically obvious; microscopic areas of **agenesis** or **atresia** may also occur (**Kroovand** and **Perlmutter**, 1981)(19).

The more severe the **ductal** abnormality, the more severely reduced is the total germ cell count in the associated **cryptorchid** testis (**Gill et al.,** 1987). Although the significance of these **ductal** abnormalities with regard to sperm capacitation and transport is uncertain, in addition to correlating with **cryptorchid** testis histology,
their impact on surgical correction of the cryptorchid testis is very clear.

When the testes is not evident upon inguinal exploration, the presence of a patent process vaginalis suggests that an intraabdominal rather than a ‘Vanishing testis’ may exist. Intraperitoneal exploration becomes mandatory.

The findings suggest that although some cases of cryptorchidism are associated with anatomic abnormalities preventing descent, most appear to be associated with hormonal abnormalities that demonstrate histologic correlates. Primary LH deficiency resulting in Leydig cell atrophy and impaired testosterone secretion may be the cause of germ cell damage seen early on and of the subfertility seen in treated cryptorchid individuals later in life.

The severity of the abnormality does not always correlate with the degree or duration of the maldescent; although generally the more
severe abnormalities are seen in those **intraabdominal** testis detected only in later adolescence.

Clinically decreased fertility is a well known consequence of **cryptorchidism**. Even after **orchiopexy**, fertility is impaired in 50-70% of **unilateral** and 80% of **bilateral** cases; approaching 100% in **B/L intraabdominal** testes.

The most important pioneering work about **histopathology** predicting the future fertility potential and risk in the development of malignancy in the form of intra-tubular **germ cell neoplasia** has been done by Nistal etal (1980)(21) (2007)(22).

In pubertal biopsies from **cryptorchid** cases, abnormalities of testicular parenchyma were classified into 4 types, according to the **morphometric** parameters comprised by estimation of **Mean Tubular Diameter** (MTD), **Tubular Fertility Index** (TFI) (no. of germ cells per tubule), and **Sertoli Cell Index** (SCI) (no. of sertoli cells per tubule).

The normal prepubertal testis will show a **mean tubular diameter** of **80-90 microns** and more than **90%** of the tubules showing **spermatogonia** and the number of **sertoli** cells will be **40±5 at birth**,
which gradually decreases and becomes $10 \pm 2$-3 at puberty and adulthood, (Nistal et al., 1980)\textsuperscript{(22)}, Human pathology.

The histology of cryptorchid testes, in addition to showing alterations in Mean Tubular Diameter (MTD), Tubular Fertility Index (TFI), and Sertoli Cell Index (SCI), may also have the following features like clustering of tubules, microcalcification, hyalinisation of the basement membrane of seminiferous tubules, as well as abnormal shapes of the tubule, like ring tubules, calcospherules and interstitial fibrosis, (Nistal et al, 1980)\textsuperscript{(22)}. In later life it may give a ‘sertoli cell only’ picture.

**Classification of cryptorchid testes based on morphometric parameters.**

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
<th>MTD ($\mu$) (Mean Tubular Diameter)</th>
<th>TFI(%) (Tubular Fertility Index)</th>
<th>SCI (Sertoli Cell Index)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Slight alteration</td>
<td>70-90</td>
<td>&gt;50</td>
<td>Normal</td>
</tr>
<tr>
<td>II</td>
<td>Marked germinal hypoplasia</td>
<td>60-70</td>
<td>30-50</td>
<td>Normal</td>
</tr>
<tr>
<td>III</td>
<td>Severe germinal hypoplasia</td>
<td>&lt;60</td>
<td>&lt;30</td>
<td>decreased</td>
</tr>
<tr>
<td>IV</td>
<td>Sertoli cell only picture</td>
<td>&lt;60</td>
<td>&lt;30</td>
<td>Immature sertoli cell hyperplasia</td>
</tr>
</tbody>
</table>
Nistal et al (2007) in their study of post pubertal biopsies came to the conclusion that type III & Type IV lesions during the prepubertal period are likely to be followed in adults with testicular lesion such as Incomplete spermatogenesis, Mixed tubular atrophy, and lesions of the basal compartment of seminiferous tubule, foretelling a worse prognosis even for IVF. They, in their studies concluded, from pubertal cryptorchid testicular biopsies prognosis concerning fertility in adulthood can be predicted.

**Malignancy and Intra-tubular germ cell neoplasia:**

Individuals born with an undescended testis have an approximately **40 fold** increased incidence of testicular malignancy over those of scrotal testes.

Approximately **10%** of all testicular tumours develop in individuals with a **history of UDT**. The incidence of malignant transformation increases with the higher location of Undescended estis, with a tumour occurring **4 times** more likely in abdominal than inguinal testes.
Testicular biopsy at the time of orchiopexy may reveal Carcinoma-in situ in both the undescended and the descended contralateral testes; and is more common in the intraabdominal than an inguinal one. However such pre-malignant changes (intra-tubular germ cell Neoplasia) may not be seen in cryptordid boys in the prepubertal age group.

Theories Postulated to the downward migration of testes are:

(Theories of testicular descent)

1. Traction by gubernaculum
2. Differential body growth
3. Increased intraabdominal pressure
4. Epididymal differentiation theory
5. Hormonal influences (MIS, Insl.3, descendin and pituitary or placental gonadotropin deficiency)
6. Androgen dependent action of genitofemoral nerve (CGRP)
7. Presence of maternal estrogens
8. Epididymal growth factor
**Risk factors:**

1. Maternal obesity
2. Caesarian section
3. LBW birth weight
4. Prematurity
5. Tendency towards miscarriages, missed abortion and decreased fertility
6. Familial-14% (Multifactoral) – autosomal dominance with incomplete penetrance
7. Environmental factors: a) Diethyl stilbesterol
   b) DDT
   c) Industrial surfactants
   d) Natural phytoestrogens (Soya beans)

**Diagnosis:**

1. Prenatal history of Hormonal ingestion
2. Family history of UDT or hormonal disorders.
3. Previous history of descended testes (to R/O ascending tests)
4. Prior inguinal hernia surgery
5. Physical examination
   a) Presence or absence of normally developed scrotum
   b) Contralateral testicular hypertrophy (Non specific)
   c) Examination in sitting/Squatting position to look for lowermost possible position in Scroterm
   d) Evidence of intersexuality
**Associated anomalies:**

1. Microcephaly
2. Prune belly syndrome
3. Post-urethral valve
4. Gastrochisis/Exomphalos
5. Bladder Extrophy
6. Neural tube defects
7. Separation of epididymis and vas.

**Complication:**

1. Decreased fertility
2. Malignancy
3. Trauma
4. Torsion
5. Inguinal hernia
6. Psychological anxiety.

**Investigation:**

1. Physical examination
2. USG
3. CT Scan/MRI
4. Diagnostic laparoscopy
5. Aortography, selective gonadal arteriography and venography-not routinely used.
**Indication for treatment:**

1. Protection of future fertility
2. Possible prevention of malignancy and its early detection
3. Correction of associated hernias and Torsion

**Management options:**

1. **Hormonal:** more successful in Retractile and B/L UDT with hormonal basis.

2. **Surgery:**
   
   a) Standard orchiopexy (single or two stage)
   
   b) Laparoscopic assisted orchiopexy
   
   c) Orchidectomy – selected cases
   
   d) Testicular prosthesis following orchidectomy.
AIM OF THE STUDY

To evaluate the histopathological changes in undescended testes with relation to age and location of the testis in testicular biopsies taken during orchiopexy, which can be helpful to prognostigate on future fertility, and also to look for the presence or absence of intra-tubular germ cell neoplasia.
MATERIALS AND METHODS

This prospective study was done from October 2005 to March 2007 over a period of 18 months, in the Department of Pediatric surgery with the assistance of the Department of Pathology, the Institute of Child Health and Hospital for Children, Madras Medical College, Chennai.

During the above period, testicular biopsies in cases of undescended testes, either unilateral or bilateral undergoing orchiopexies were done on 21 children with 28 biopsy specimens, varying in age from 10 months-10 years.

Inclusions criteria : All cases of Undescended testis
Exclusive criteria : Retractile and Ectopic testis.

The specimens were fixed in Bouin’s solution (saturated aqueous picric acid 75 ml, 40% formaldehyde-25ml, and glacial acetic acid-5ml) for at least 6 hours for complete fixation, and subjected for histopathological examination.
After routine processing, sections of 4-5 micron thickness were made and stained with Hematoxylin and Eosin (H&E) and Masson Trichrome (MTS); viewed under microscope and analysed. Semithin sections were also taken and studied to look for the presence of spermatogonia.

Sections were analysed for the number of seminiferous tubules, diameter of the seminiferous tubules, presence of sertoli cells with or without hyperplasia, presence of spermatogonia and the presence or absence of intra-tubular germ cell neoplasia. Morphometric analysis of the tubules were done using image analyzer using the Software (Image Pro plus 6) after measuring 50 tubules per section. Peritubular fibrosis, calcification, macrophages and hyalinization were also analysed.

**The following analysis made:**

1) **Tubular fertility Index**: defined as percentage of tubules containing germ cells
2) **Mean Tubular diameter**: measured on 50 tubules per cross section using the image analyser.
3) **Sertoli cell Index**: Mean number of sertoli cells per tubule.
These indices were calculated and compared with reference values published by Nistal and Pagnigua, in the Journal of Human Pathology, 1980 and were classified into 4 types based on these indices.

**TYPE I** : Minimal alteration

**TYPE II** : Marked germinal hypoplasia

**TYPE III** : Severe germinal hypoplasia

**TYPE IV** : Immature Sertoli cell hyperplasia with no Germ cells.
RESULTS

28 testicular biopsies were taken from 21 children undergoing orchiopexy either for unilateral or bilateral testes.

Youngest child: 10 months

Oldest child: 10 years

Of the 21 children, 7 had B/L undescended testes, totalling for 28 biopsies.

The following results were observed:

A) BASED ON TYPE:

<table>
<thead>
<tr>
<th>Type</th>
<th>Number</th>
<th>Age (Years)</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Intraabdominal</td>
</tr>
<tr>
<td>I</td>
<td>6</td>
<td>1¼ – 6</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(1¼; 1¼ 1½; 6)*</td>
</tr>
<tr>
<td>II</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>III</td>
<td>8</td>
<td>1¼ -8</td>
<td>3 (3;3;7)*</td>
</tr>
<tr>
<td>IV</td>
<td>9</td>
<td>10/12-10</td>
<td>3 (10/12; 1;7)*</td>
</tr>
<tr>
<td>Vanishing Testis</td>
<td>5</td>
<td>2¼-10</td>
<td>(2¼;3;5;8;10)*</td>
</tr>
</tbody>
</table>

* Indicates the age of each child in that particular group.
### B) Relationship between age, location and the type:

#### CANALICULAR: (n=13)

<table>
<thead>
<tr>
<th>Type</th>
<th>Age</th>
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<tbody>
<tr>
<td></td>
<td>0-1 Yrs</td>
<td>1-2 Yrs</td>
<td>2-5 Yrs</td>
<td>5-10 Yrs</td>
</tr>
<tr>
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<td>0</td>
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<td>1</td>
<td>0</td>
</tr>
<tr>
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<td>1</td>
</tr>
<tr>
<td>Type IV</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>2</td>
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#### ABDOMINAL: (N=10)

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<td>0-1 Yrs</td>
<td>1-2 Yrs</td>
<td>2-5 Yrs</td>
<td>5-10 Yrs</td>
</tr>
<tr>
<td>Type I</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Type II</td>
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<td>0</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Type IV</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Normal histology comprising a Mean Tubular Diameter of 90 or >90 microns, Tubular Fertility Index of >50% and Sertoli Cell Index corresponding to the age was not observed in any of the 28 testicular biopsies.
Among all the 28 specimens showing alterations, there were 6 Type I lesions (4 Intraabdominal; 2 canalicular), no Type II lesion, 8 Type III lesions (3 intraabdominal; 5 canalicular), 9 Type IV lesions (3 intraabdominal; 6 canalicular) and 5 ‘Vanishing testis’ (nubbins with blind ending vas and spermatic vessels with no evidence of seminiferous tubules, leydig cells or sertoli cells).

Hyalinization of seminiferous tubules, presence of calcification, macrophage, along with peritubular fibrosis were observed in 3 Type IV lesions and none in other types.

2 cases among the 5 vanishing testis presenting as nubbins showed peritubular fibrosis and calcifications.

Intracanalicular testis (palpable) contributed to (13 nos); 2 were Type I, 5 Type III and 6 Type IV, and none in Type II.

Intraabdominal (Nonpalpable testis) contributed (10 nos), excluding the 5 Vanishing testes; 4 were Type I, 3 Type III and 3 Type IV and no Type II lesions.
### COMPARISON AMONG THE VARIOUS AGE GROUPS

<table>
<thead>
<tr>
<th>Age</th>
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<th>Nos.</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Intraabdominal</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Canaliclar</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1 Yr.</td>
<td>1</td>
<td>IV</td>
<td>1</td>
</tr>
<tr>
<td>1-2 Yrs.</td>
<td>3, 1</td>
<td>I, III, IV</td>
<td>4, 1, 5</td>
</tr>
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<td>2-5 Yrs.</td>
<td>-</td>
<td>I</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>2, 31</td>
<td>III</td>
<td>5</td>
</tr>
<tr>
<td>5-10 Yrs.</td>
<td>-</td>
<td>I</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>1, 1</td>
<td>III, IV</td>
<td>2, 3</td>
</tr>
</tbody>
</table>

There was **no evidence** of any tubule showing **intra-tubular** germ cell neoplasia.
DISCUSSION

A study of Prepubertal Cryptorchid testicular biopsy typically includes the measurement of Mean Tubular Diameter, Tubular Fertility Index and Sertoli cell Index.

They are classified as Type I (minimal alterations) with MTD: 70 - 90 µ; TFI > 50%; and with normal number of sertoli cells (SCI) per seminiferous tubule.

Type II (marked germinal hypoplasia) with MTD: 60-70 µ; TFI: 30-50%; and normal SCI.

Type III (severe germinal hypoplasia) described as testis with MTD: <60 µ; TFI: <30% and decreased sertoli cells.

Type IV as lesions with MTD: <60 µ; TFI <30%; along with the presence of ‘immature sertoli cell’ hyperplasia. ‘Vanishing testis’ were described as nubbins of testicular tissue with only a blind
ending vas and spermatic vessels on it, with no evidence of either seminiferous tubule, leydig cells or sertoli cells.

We tried to establish a correlation between the histological type of testicular lesion and the age at which orchiopexy is done, as well as the location of the testes. All the four histological types of lesions were observed in all the age groups and in all the location from the intraabdominal region to the canalicular region from 10 months to 10 years.

In our study changes start occurring as early as 10 months from a child operated on that age showing a type IV lesion and these type IV lesions were reported in 5 out of 10 cases (50%) between 1-2 years, 4 being canalicular.

The severity of the type of lesion should increase as age advances in general, but our study showed only 3 children out of 9 with type IV lesion (33.3%), probably because of the small study population.
Those type IV lesion which are found in older children in the age group of 5-10 years showed relatively more frequent presence of microcalcification, hyalinization and interstitial fibrosis.

No evidence of intra tubular germ cell neoplasia was present in any of the children.

The only drawback of the study was that we were not able to get age matched control biopsy specimens from normal testis. Therefore we had used the normal measurements published in the literature by Nistal et al, 1980 in Human pathology as reference values.
CONCLUSION

• In our histopathological study of testicular biopsies at the time of orchiopexy, it though showed that all the types of testicular lesions are present in all locations from the intraabdominal to the canalicular region, these changes start occurring as early as 1 year of life and even earlier for eg. (10 months in one child in our study) with more severe lesion type. Therefore the generally recommended timing of orchiopexy now being as 1 year can be reduced even to a still further lower age group.

• Classification of prepubertal testis by their histologic type could make it possible to grade the prognosis with regard to fertility in a large numbers of patients who undergo Orchiopexy at an earlier age.
• Such studies of **prepubertal cryptorchid biopsies** comparing them with **post pubertal testicular biopsies** in laterlife a larger number of cases definitely will help in **predicting future fertility**.

• Also in prepubertal cryptorchid testicular biopsies, it is also possible look for the presence of **intra-tubular germ cell neoplasia**.
<table>
<thead>
<tr>
<th>No</th>
<th>AGE (Yrs)</th>
<th>Location</th>
<th>MTD (µ)</th>
<th>TFI (%)</th>
<th>SCI</th>
<th>TYPE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intraabdominal</td>
<td>Canalicular</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1¼ (L) Intraabdominal</td>
<td>(R) Intraabdominal</td>
<td>&gt;70</td>
<td>&gt;50%</td>
<td>N</td>
<td>I</td>
</tr>
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<td>1¼</td>
<td>(L) Intraabdominal</td>
<td>(R) Intraabdominal</td>
<td>&gt;70</td>
<td>&gt;50</td>
<td>N</td>
</tr>
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<td>(L) Canalicular</td>
<td>(R) Intraabdominal</td>
<td>90</td>
<td>&gt;50</td>
<td>N</td>
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<tr>
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<td>&gt;60</td>
<td>&gt;60</td>
<td>N</td>
<td>I</td>
</tr>
<tr>
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<td>80</td>
<td>&gt;60</td>
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<td>I</td>
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<td>(R) Canalicular</td>
<td>47</td>
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<td>(R) Canalicular</td>
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<td>Immature sertoli cell hyperplasia</td>
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<td>(R) Intraabdominal</td>
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<td>&lt;10%</td>
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</tr>
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<td>(R) Intraabdominal</td>
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<td>N</td>
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<td>(R) Canalicular</td>
<td>50</td>
<td>20%</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>1¼</td>
<td>(L) Canalicular</td>
<td>(R) Canalicular</td>
<td>50</td>
<td>20%</td>
<td>N</td>
</tr>
<tr>
<td>8</td>
<td>4</td>
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<td>52</td>
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<td>Low</td>
<td>III</td>
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<td>9</td>
<td>7</td>
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<td>(R) Canalicular</td>
<td>&lt;50</td>
<td>&lt;10%</td>
<td>N</td>
</tr>
<tr>
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<td>(R) Canalicular</td>
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<td>&lt;10%</td>
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<tr>
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<td>50</td>
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<td>No</td>
<td>AGE (Yrs)</td>
<td>Location</td>
<td>MTD (µ)</td>
<td>TFI (%)</td>
<td>SCI</td>
<td>TYPE</td>
</tr>
<tr>
<td>----</td>
<td>----------</td>
<td>-----------------</td>
<td>---------</td>
<td>---------</td>
<td>----------------------------------------------------------------------</td>
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</tr>
<tr>
<td>11</td>
<td>1</td>
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<td>50</td>
<td>&lt;10%</td>
<td>Low, with Immature sertoli cell hyperplasia</td>
<td>IV</td>
</tr>
<tr>
<td>12</td>
<td>1½</td>
<td>(R) Canalicular</td>
<td>50</td>
<td>&lt;10%</td>
<td>Low, with Immature sertoli cell hyperplasia</td>
<td>IV</td>
</tr>
<tr>
<td>13</td>
<td>1½</td>
<td>(L) Canalicular</td>
<td>50</td>
<td>&lt;10%</td>
<td>Low, with Immature sertoli cell hyperplasia</td>
<td>IV</td>
</tr>
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<td>14</td>
<td>1¼</td>
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<td>50</td>
<td>&lt;10%</td>
<td>Immature sertoli cell hyperplasia</td>
<td>IV</td>
</tr>
<tr>
<td>15</td>
<td>7</td>
<td>(L) Canalicular</td>
<td>&lt;50</td>
<td>&lt;10%</td>
<td>Immature sertoli cell hyperplasia with Hyalanisatiation</td>
<td>IV</td>
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<tr>
<td>16</td>
<td>8</td>
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<td>54</td>
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<td>Immature sertoli cell hyperplasia with Hyalanisatiation</td>
<td>IV</td>
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<tr>
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<td></td>
<td>(R) Canalicular</td>
<td>54</td>
<td>&lt;10%</td>
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</tr>
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<td>2¼</td>
<td>(L) Non Palpable</td>
<td>Nubbins</td>
<td>-</td>
<td>-</td>
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</tr>
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<td>18</td>
<td>3</td>
<td>(L) Non Palpable</td>
<td>&quot;</td>
<td>-</td>
<td>-</td>
<td>Vanishing testis</td>
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<td>Location</td>
<td>MTD (µ)</td>
<td>TFI (%)</td>
<td>SCI</td>
<td>TYPE</td>
</tr>
<tr>
<td>----</td>
<td>-----------</td>
<td>------------------</td>
<td>---------</td>
<td>---------</td>
<td>-----</td>
<td>-------------------------------------------</td>
</tr>
<tr>
<td>19</td>
<td>5</td>
<td>(L) Non Palpable</td>
<td>“</td>
<td>-</td>
<td>-</td>
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<td>8</td>
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<td>2 tubules with 100</td>
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<td>-</td>
<td>Vanishing testis with Peritubular Fibrosis Hyalinization</td>
</tr>
<tr>
<td>21</td>
<td>10</td>
<td>(R) Non Palpable</td>
<td>&gt;90 Very few</td>
<td>-</td>
<td>-</td>
<td>Vanishing testis with Peritubular Fibrosis Hyalinization</td>
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</table>
PROFORMA

Name:    Age:    IP No.

DOA:     DOS:     DOD:

Informant:    Reliability:

Complaints:
1. Palpability of testis: Palpable / Nonpalpable
    Unilateral / Bilateral
2. Scrotal development:
3. Evidence of Intersexuality
4. Prenatal History:
   Family History
   Previous H/O: Testicular descent
   Surgery
   Hormonal treatment

Associated anomalies

Risk factors

HPE: 1) MTD: 2) TFI: 3) SCI:
    4) Type:
BIBLIOGRAPHY


7) Smail: Paed Andrology, Vol.7; 1981


16) Cooper: Journal of anatomy 64:5, 1929


TYPE III

LOW POWER VIEW

HIGH POWER VIEW
TYPE III

SCANNER VIEW

LOW POWER VIEW

HIGH POWER VIEW
TYPE IV

SCANNER VIEW

HIGH POWER VIEW
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<th>Technique</th>
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<th>Pedal edema</th>
<th>Abd. discomfort</th>
<th>NYHA class</th>
<th>Dyspnoea</th>
<th>Preop V/S ratio</th>
<th>CT PE</th>
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<th>CT Peri ca</th>
<th>LV Dimension(cm)</th>
<th>CVP</th>
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<th>Post op inotropes</th>
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<td>f</td>
<td>15/9/05</td>
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<td>III 6</td>
<td>pre</td>
<td>pre</td>
<td>pre</td>
<td>y</td>
<td>15</td>
<td>0.56</td>
<td>pre</td>
<td>10mm</td>
<td>calcific</td>
<td>LVF</td>
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<td></td>
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<td>26</td>
<td>m</td>
<td>24/10/05</td>
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<td>III 5</td>
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<td>pre</td>
<td>y</td>
<td>12</td>
<td>0.55</td>
<td>pre</td>
<td>10mm</td>
<td>y</td>
<td>n</td>
<td></td>
<td></td>
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<td></td>
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<td>pre</td>
<td>y</td>
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