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Non Syndromic Multiple Keratocystic Odontogenic Tumour Occurring in Both the Jaws: Case report and Review of Literature

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Abstract: *Keratocystic odontogenic tumour (KCOT) are the one of the most common form of cystic lesions affecting the maxillofacial region. Multiple keratcystic odontogenictumour are known to occur in a wide range of syndrome, the most common among them being nevoid basal cell carcinoma syndrome(NBCCS). A case of multiple KCOTS in a non syndromic case in a ten year old female patient is being presented here which had been successfully managed so far without recurrence.*

Keywords: *Kerocysticodontogenic tumour(KCOT), nevoid basal Cell carcinoma Syndrome(NBCCS),gorlin Goltzsyndrome, Odontogenic Keratocyst(OKCs*)

I. Introduction

Keratocysts (OKCs) are the one of the most common form of cystic lesions affecting the maxillofacial region. They are clinically aggressive lesions which are thought to arise from the dental lamina or its remnants. The OKC was first described in 1876, and named by Phillipsen in1956. It is one of the most aggressive odontogenic cysts of the oral cavity.[1]

Usually, multipleKeratocystic Odontogenic Tumors (KCOTS) occur as a component of NBCCS which was first described by Gorlin and Goltz in 1960; hence also called Gorlin-Goltz syndrome. [1]
This study presents a rare case of multiple KCOT in a non-syndromic case with a long term follow up.

II. Case Report

A 10 year old female patient was referred to our institute with a chief complaint of swelling in upper jaw on right side with a history of a slowly progressive swelling since 3 to 4 months. The patient was subjected to thorough evaluation.

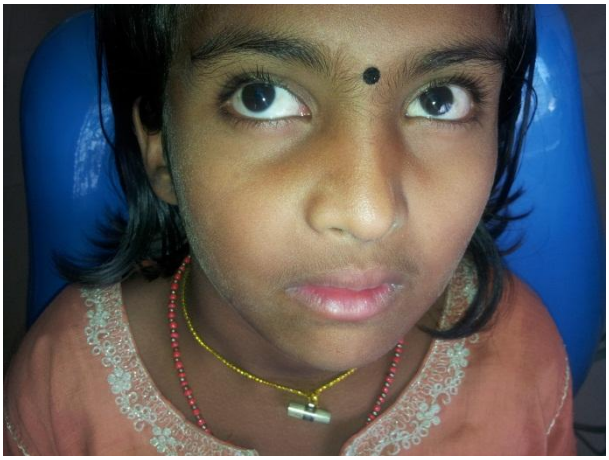

Fig1: Extra oral appearance

General physical examination revealed no physical and mental abnormalities.

Local examination, extra orally revealed a solitary sessile, diffuse swelling on right infra orbital region with obliteration of the right naso-labial fold. Skin over the swelling was normal, firm to hard on palpation without any fluctuation. The swelling was slightly tender on palpation without any local rise in temperature.

Intra orally examination revealed laterally tipped right central incisor and incompletely erupted central incisor on the left side with missing permanent lateral incisors bilaterally in the maxilla along with the obliteration of labio-buccal sulcus on the right side.

In the mandible all the incisors were missing except for partially erupted central incisor on the left side. The respective permanent teeth relevant to the age were missing on examination

Intra oral appearance

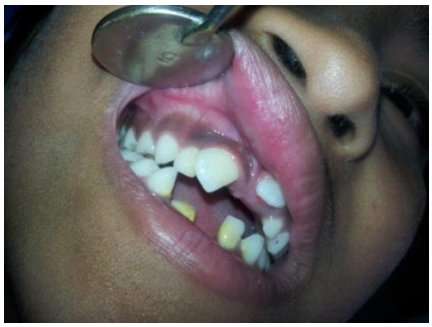

Fig 2: Upperbuccal sulcus

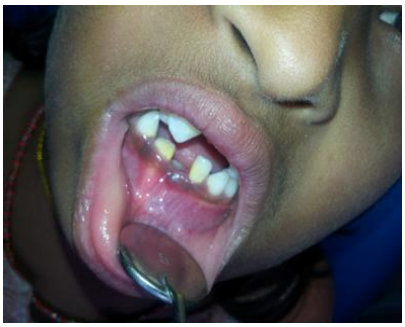

fig 3: lower buccal sulcus

Aspiration yielded a straw colored fluid.

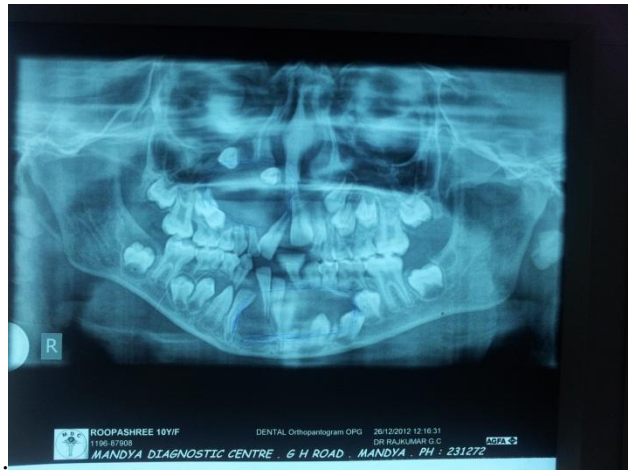

Fig 4: OPG of the patient

OrthoPantamo Gram was advised which revealed following features.

In the right maxilla, a solitary unilocular,diffuse radiolucency roughly ovoid in shape, with a sclerotic border with impacted lateral incisor and canine along the superior half of the radiolucent lesion and premolars pushed laterally along the sclerotic border was established.

In the mandible the radiolucent lesion was roughly ovoid, unilocular, and present in the parasymphyseal region along with the presence of multiple impacted teeth which included central and lateral incisors and canines bilaterally was noticed inside the radiolucent defect. Radiolucency was surrounded by a sclerotic border.

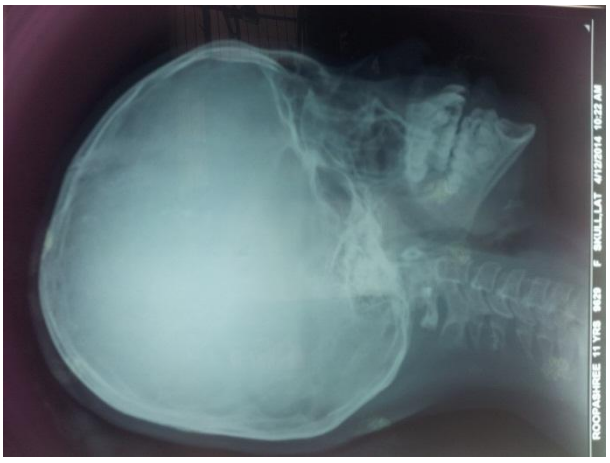

Fig 5: lateral view of the skull

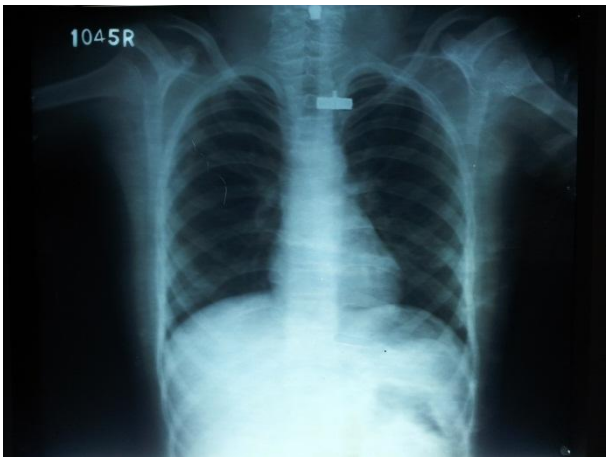

Fig6: chest radiograph

In view of the multiple appearances of the cysts, chest radiograph (fig 6)to rule out bifid ribs and skull radiograph fig(5) to rule out presence of any intra cranial calcification was advised and both views revealed no suggested abnormalities and these above mentioned findings lead to a provisional diagnosis of multiple dentigerous cyst. The patient was treated by enucleation for both the lesions under General Anesthesia following which lesion was sent for histo-pathology for final evaluation.

The histopathological evaluation described a cystic cavity lined by corrugated parakeratinised stratified squamous epithelium about 6-8 layers thick with basal cell layer showing columnar cells with nucleus palisading and reversal polarity. The connective tissue showed loose bundles of collagen fibers, inflammatory cells predominantly composed of lymphocytes and numerous blood vessels lined by endothelial cells the clinical and histopathological features are suggestive of KeratoCysticOdontogenicTumour.KCOT(illustrated in the figure 7-12)

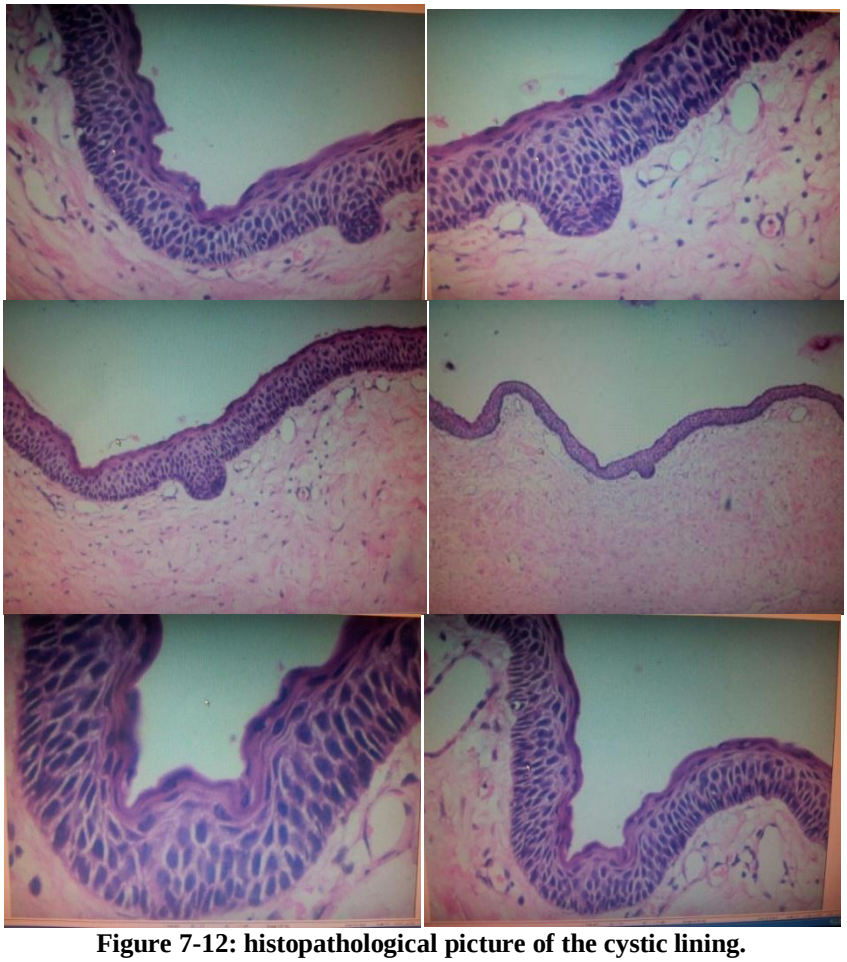

Figure 7-12: histopathological picture of the cystic lining.

III. Discussion

OKC is a common developmental odontogenic cyst and its biologic behavior is similar to a benign neoplasm. Therefore, in the latest WHO classification of odontogenic tumors in 2005, it has been given the term Kerato Cystic Odontogenic Tumour(KCOT).In Who 2005 edition of its histological classification of odontogenictumors, keratocystic odontogenic tumor commonly known as odontogenic keratocyst has been defined as " a benign uni-multi cystic intra- osseous tumour of odontogenic origin with a characteristic lining of parakeratinised stratified squamous epithelium and potential for aggressive infiltrative behaviour[4]

KCOT may be found in any age with peak prevalence between 10 to 40 years old with a marked tendency to occur in the posterior body and ascending ramus of the mandible where usually 60- 80% of cases are known to occur[2].Small KCOTs are usually asymptomatic but larger ones may show clinical manifestations like pain, swelling or drainage.[2]

Radiologically, KCOTs demonstrate a well-defined radiolucent area with smooth and often corticated margins and may be unilocular or multilocular. In 25 to 40% of cases, an unerupted tooth is seen in association with the lesion [2]. In the reported case both mandible and maxilla was involved, revealing only a maxillary swelling has a presenting feature, age of the patient being 8 to 9 years old and the radiological appearance is as below along with multiple unerupted teeth.

Mandibular lesion showed a unilocular radiolucency present in the parasymphsiseal region involving unerupted canine and lateral incisors bilaterally along with left 1st premolar. In maxilla, a unilocular radiolucent lesion in relation with unerupted premolars along with lateral incisor and the canine of the right side of the maxilla surrounded by well corticated margins.

In this case, microscopic evaluation of the mandibular lesion showed characteristic features of KCOT inducing a corrugated parakeratinized stratified squamous epithelial lining with palisaded basal cell layer without rete ridge formation.

Several sections were prepared to achieve the correct diagnosis.
Finally, the diagnosis of KCOT was established for both cystic lesions.

The relationships of multiple dental cysts with other abnormalities have been noted in the literature since 1930 but it was left to Gorlin and Gotz in 1960 to tie all this together into the syndrome that currently bears the name.[5]

But multiple KCOTs are also known to be a component of Gorlin- Goltz syndrome or NBCCS, orofacial digital syndrome , Ehler- Danlos syndrome , Noonan syndrome or other syndromes.[2]

NBCCS, Basal cell nevus syndrome (BCC), (Gorlin's syndrome, or McKusickMendelian Inheritance in Man 109400) was first described by Jarisch and White in 1894.[1] He used the term epithelioma adenoids cysticum for this combination. Later in the year 1960, Gorlin-Goltz established the association of basal cell epithelioma, jaw cyst and bifid ribs, a combination which is now frequently known as Gorlin-Goltz syndrome as well as NBCCS. The characteristics may include basal cell carcinomas, multiple OdontogenicKeratocysts (OKCs), palmar and/or plantar pits, and ectopic calcifications of falxcerebri. These features are considered major diagnostic criteria. More than 100 minor criteria have been described, including cardiac and ovarian fibromas, mild mandibular prognathism, frontal and bilateral bossing, and others. Although NBCCS is associated with multiple OKCs, it does not imply that a patient should have more than one cyst at a given point in time; rather it refers to the lifetime history of the patient. Single or multiple OKCs in the absence of other features of NBCCS may also be considered an incomplete form of this syndrome.[3]

Although GorlinGoltz syndrome is primarily recognized by multiple basal cell carcinomas, it was not evident in the above mentioned patient.
The occurrence of basal cell carcinomas is only in 50% of the cases.[5]

Molecular Basis of the Behaviour Associated With Kcot

Mutations in the tumor suppressor gene PTCH are identified as the underlying genetic events in NBCCS. It has been proposed that the development of an OKC would follow the "2-hit" hypothesis. According to this hypothesis, OKCs present in NBCC arise from precursor cells that contain a hereditary "first hit," and the allelic loss represents loss of the normal allele while sporadic OKC might arise from susceptible cells in which two somatic "hits" have occurred. Shear suggested that two cysts from one syndrome patient that occurred on opposite sides of the mandible had the same pattern of allelic loss, suggesting that this genetic mutation occurred at a very early stage of embryogenesis.[3]

Shear also added that the possibility that knutsons "two hit hypothesis of cancer development" may also explain the transformation of KCOT into neoplasia.[6]

Parakeratinization and satellite cysts common to sporadic cysts are even more common to syndromic counterparts. It has been shown that keratocysts, when associated with NBCCS, show a higher number of

satellite rests of tumor and more solid areas of epithelial proliferation and odontogenic epithelial rests within the fibrous capsule than is found in sporadic type. [3]

Proliferative activity of the odonto genic epithelium in cystic lesions was examined by immunolabelling of ki67, EGF, and survinin .It was found that proliferation rate of KCOT was greater than dentigerous cyst. In KCOT the epithelial cell showed neoplastic proliferative compartment, maintained by inhibition of apoptosis. Angiogenesis was assessed in KCOT, dentigrous cyst and normal mucosa using cd 105 antigens. It was demonstrated that cd 105 antigen is strongly expressed in microvasculature of KCOT compared to dentigerous cyst and normal mucosa. Thus suggesting, the cyst wall of the KCOT may also play a role in neoplastic behavior of the lesion. These findings can further support the WHO decision recommending the term KCOT as it better reflects the neoplastic behavior.[6]

Clinical Behaviour Of Kcots

The biological behavior of OKCs associated with NBCCS is more aggressive and these cysts have higher recurrence rates (82%) compared with solitary keratocysts (61%). The higher recurrence rates are attributed to epithelial remnants of the cystic lining or satellite cysts left behind following surgery. A recurring OKC can be a new cyst that originates from epithelial residue or a microcyst left behind in the overlying mucosa. This is reinforced by the fact that OKCs can occur in bone grafts if the overlying mucosa is not excised. The term "multiple cysts" does not necessarily mean that the patient must have more than one cyst at a given time; rather it refers to occurrence of cysts over the lifetime of the patient. [1]

It is a well-known fact that cysts associated with unerupted teeth occur only in few individuals, whereas unerupted teeth are common occurrence. This suggests that some people are prone to cyst formation. A genetic predisposition may always be a possibility. This also suggests that our patient might have a predisposition for jaw cysts[1]

Rarely, multiple KCOTs are seen without other syndromic manifestations Brannon reported that 5.8 percent of 312 cases of KCOTs, had multiple cysts without any syndromic manifestations.[2]

However, except for presence of KCOTs, our patient was healthy in clinical examinations and suggestive features of these syndromes such as basal cell carcinoma, skeletal or orofacial defects, stunted growth, bleeding diathesis, hyper-extensible skin and hypermobile joints and other features were not present.

Similar cases to the current case have been reported in a few published English articles.

Auluck et al. ,Sholapurkur et al. ,Parikh ,Bartake et al. Guruprasad et al. have reported their experiences regarding the incidence and management of such cases not associated with any of the mentioned syndromes.[2]

Also, findings of Habibi et al. study on Iranian populations showed that 8.1% of 83 cases with KCOTs were associated with NBCCS and 7.6% of them had recurrence, but none of the cases with multiple KCOTs were non-syndromic.[2]

There is a little information about the relationship between cell proliferative markers and the recurrence rate of KCOTs. The study performed by Kuroyanagi et al. showed that ki- 67 expression, at time of diagnosis, may act as a prognostic marker. Multiple KCOTs might be the first and the only manifestation of NBCCS without any other features associated with syndrome. However, other symptoms can occur in later decades of life.[2]

Treatments for KCOT are generally classified as either aggressive or conservative. The goal is to choose the right modality carrying the lowest risk of recurrence and least morbidity. And at the same timerestoring the morphology and function of the affected area

Therapeutic interventions of KCOT include marsupialization and enucleation, combined with adjuvant cryotherapy with Carnoy's solution, and marginal or radical resection.

To enucleate is "to remove whole or clean, as a tumour from its envelope." Curettage is defined as "the removal of growths or other material from the wall of a cavity .Enucleation would be treatment of choice. It is a one stage surgical procedure followed by repeated changes of bismuth iodine paraffin paste pack .Repeated periodic radiographic examination at regular interval so as to analyse the regeneration of the bone into the defect[4]

Stolingea ,Voorsmit and colleagues advocated excision of the overlying mucosa and have popularized the use of Carnoys solution as a chemical fixative. Carnoys solution contains ferric chloride,absolutealcohol,chloroform,glacial acetic acid that that penetrates to a predictable time dependant depth at the same time neurovascular bundle being protected with a coat of Vaseline. The application is done for 5 minutes which results in bone penetration of 1.54mm nerve penetration up to a depth of .15mm and mucosal depth of 5mm. [5]

Cryosurgery involves the use of liquid nitrogen which possesses a unique ability to devitalize the bone in situ while leaving the inorganic framework untouched. Both these techniques are advocated in killing the any

epithelial remnants and dental lamina within osseous keratocysts thus helping in reducing the rate of recurrences.[3]

According to Blanas N et al., simple enucleation was reported to have a recurrence rate of 17% to 56% while simple enucleation combined with adjunctive therapy, such as the application of Carnoy's solution or decompression before enucleation, was reported to have recurrence rates of 1% to 8.7% [4]

But in the presented case the approach was radical so as to eliminate the risk of recurrence therefore the involved teeth were removed along with enucleation was considered as the treatment of choice keeping in view the age of the patient; which was followed up with repeated periodic bimonthly checkup so as to change the residual dead space defect with iodoform pack at the same time to ensure complete healing occurs by secondary intention. Bimonthly changing of the pack ensured clinical assurement in progress of the healing. Repeated periodic radiographs has ensured complete bone reformation of the defect .In a span of 1 year 9 months there was complete growth of solid healthy bone into the bone defect without any clinical or radiological signs of recurrence which was ascertained by orthopantamogram(fig 13)

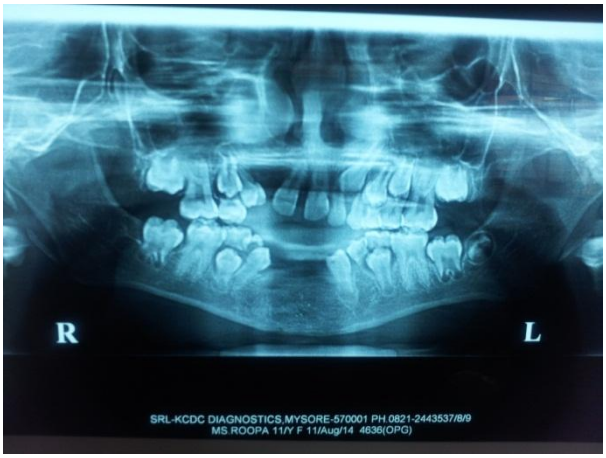

Fig 13:Recent OPG showing complete regeneration of the bone into the defect in both the jaws

Unlike in other cases of KCOT,keratin was not observed during enucleation, rather a straw colored fluid and the cystic linings of the respective cysts were noticed.

The diagnosis for the syndrome can be done clinically using the criteria suggested by Evans and others and Kimons and others However, there may be variations in the major diagnostic criteria for NBCCS in some populations due to genetic and geographic differences Our patient did not meet any of these diagnostic criteria for NBCCS. But in view of the clinical history and histopathologic correlations (Table 2), we suggest the possibility of this case being a non syndromic case involving multiple odontogenickeratocyst.

IV. Conclusion

For a pediatric dentist/Faciomaxillary surgeon

- Any patient with a KCOT, the presence of multiple KCOTs should be considered. Therefore, careful histopathologic and radiological examination for any other existing lesion should be done.
- Any patient reporting with the multiple OKCs should be evaluated thoroughly for the possibility of NBCCS as OKC/KCOT may be the first and only manifestation of this syndrome. Also for the fact that OKC/KCOT associated with this syndrome have higher rate of recurrence than the isolated OK/KCOT, a very strict follow up has to be followed for a long period of time.
- The possibility of other features of NBCCS has to be explained to the patient as well as his relatives, so as to allow appropriate genetic counselling and serial screening for the development of malignancies and other complications besides OKCs.

Acknowledgement

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Table 1: Diagnostic Criteria As Given By Kimons Et Al

MAJOR CRITERIA
More than 2 basal cell carcinomas or I ina patient <20 yrs of age
3 or more plantar pits
Bilamaller calcification of falxcerebri
Odontokeratocyst of jaws proven histopathologically
A first degree relative with NBCCS
Bifid ,fused ribs

MINOR CRITERIA
Macrocephaly
Congenital malformations,hypertelorism,cleftlip/palate,frontal bossing
Skeletal deformities,sprengeldeformity,markedpectusdeformity,syndactyly of digits
Radiological abnormalities,bridging of sellaturcica,vertebral anomalies, modelling defects of hands and feet
Ovarian fibroma or medulloblastoma

Table 2: Comparison of KCOTS associated with NBCCS and solitary/sporadic KCOTS

Histopathologicalcharacterestics

NBCCS ASSOCIATED	Sporadic/solitary KCOTS
Smaller epithelial heights	Greater epithelial height
More frequent occurrence of odontogenic Islands and daughter cysts	Led frequent occurrence of odontogenic islands
Fewer total and basal nuclei	More total and basal nucleii

Clinical characterstics

NBCCS ASSOCIATED	Sporadic KCOTS
Occurs at early age	Occur at middle order or older age
Multiple cysts	Isolated cysts
Occurs in both jaws with equal frequency	Occurs more often in lower jaws
Higher recurrence rate (83%)	Lower recurrence (61%)