SYSTEMATIC REVIEW

Keratocystic odontogenic tumour: systematic review

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Objectives: The aim of this review is to evaluate the principal clinical and conventional radiographic features of non-syndromic keratocystic odontogenic tumour (KCOT) by systematic review (SR), and to compare the frequencies between four global groups.

Methods: The databases searched were the PubMed interface of Medline and LILACS. Only those reports of KCOTs that occurred in a series of consecutive cases, in the reporting authors' caseload, were considered.

Results: 51 reports, of 49 series of cases, were included in the SR. 11 SR-included series were in languages other than English. KCOTs affected males more frequently and were three times more prevalent in the mandible. Although the mean age at first presentation was 37 years, the largest proportion of cases first presented in the third decade. The main symptom was swelling. Over a third were found incidentally. Nearly two-thirds displayed buccolingual expansion. Over a quarter of cases recurred. Only a quarter of all SR-included reported series of cases included details of at least one radiological feature. The East Asian global group presented significantly as well-defined, even corticated, multilocular radiolucencies with buccolingual expansion. The KCOTs affecting the Western global group significantly displayed an association with unerupted teeth.

Conclusions: Long-term follow-up of large series that would have revealed detailed radiographic description and long-term outcomes of non-syndromic KCOT was lacking.

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Introduction

The term odontogenic keratocyst was first used by Philipsen in 1956.¹ This lesion was recently renamed by him as keratocystic odontogenic tumour (KCOT) and reclassified as an odontogenic neoplasm in the World Health Organization's 2005 edition of its histological classification of odontogenic tumours.² According to this edition the KCOT has been defined as "A benign uni- or multicystic intraosseous tumour of odontogenic origin, with a characteristic lining of parakeratinized stratified squamous epithelium and potentially aggressive, infiltrative behaviour. It may be solitary or multiple. The latter is usually one of the stigmata of the inherited naevoid basal cell carcinoma syndrome (NBCCS)."² To emphasise the essential parakeratotic

feature of this new "tumour", it adds "Cystic jaw lesions that are lined by orthokeratinizing epithelium do not form part of the spectrum of a ... KCOT."²

Although Blanas et al³ have performed a systematic review (SR) on the odontogenic keratocyst all their SR-included reports did not distinguish between the above KCOT and the orthokeratotic type, which is now recognized as an entirely separate lesion, the orthokeratinized odontogenic cyst (OOC).⁴

Sackett et al⁵ defined an SR as a summary of the medical literature that uses explicit methods to search systematically, appraise critically and synthesize the world literature on a specific issue. This means that the SR, like any other form of primary research, will have a Materials and Methods, and a Results section.⁶

The SR has generally been applied to treatment and drug trials, but has also become a powerful tool when adapted to the clinical and radiological presentations of important oral and maxillofacial lesions.⁷

An important feature that helps to distinguish the KCOT is stated by White and Pharoah.⁸ KCOTs

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exhibit a “propensity to grow along the internal aspect of the jaws, causing minimal expansion” (see their Figure 21–15). Additionally, KCOTs associated with NBCCS occur earlier and exhibit a greater tendency to recur than non-syndromic KCOTs.⁸

Aims and research question

The principal aim was to include as many reports or pertinent parts of those reports as possible and to evaluate the principal clinical and conventional radiographic features of non-syndromic KCOT by SR.

The primary research question for this SR is “Do other clinical and conventional radiographic features improve diagnosis of non-syndromic KCOT compared with no or minimal buccolingual expansion?” This follows the four-part format required for the SR’s research question set out by MacDonald-Jankowski and Dozier.⁶ In order to include as many reports as possible a wide search of the literature was made, including non-English reports. In addition to a Medical Subject Heading (MeSH) search a “free-text” search was included supported both by hand-searching of journals, which are the natural destinations for reports on oral and maxillofacial lesions, and by reference-harvesting of those reports identified by database searches and hand-searching.

To assist in answering the above research question the SR-included reports will be divided into four global groups: Western, sub-Saharan African, East Asian and Latin American, broadly reflecting ethnic origin.

Materials and methods

Systematic review

The approach follows the SR procedure set out in earlier SRs for other oral and maxillofacial lesions. The research question is described above and the search strategy, the strategy for sifting the literature and the interpretation of the data retrieved are set out below.

The search strategy

The search was based on the research question. The databases searched were the PubMed interface of MEDLINE (National Library of Medicine) and LILACS (Literatura Latino Americana e do Caribe em Ciências da Saúde) by BIREME (Latin American and Caribbean Center on Health Sciences Information). LILACS provided access to important Hispanic publications largely not indexed by MEDLINE and has been discussed in an SR on focal osseous dysplasia (FocOD).⁹

The two MeSH terms were “odontogenic cyst” and “odontogenic tumour”. Odontogenic cyst was defined by MEDLINE as “cysts found in the jaws and arising from epithelium involved in tooth formation”. This

MeSH, first introduced in 1965, includes terms that are no longer used or are unknown to current dental and oral and maxillofacial practice. The MeSH definition contained keratocyst and keratocysts as two separate entry terms (synonyms). Odontogenic tumour was defined in 1980 as “neoplasms produced from tooth-forming tissues”. Its entry terms are odontogenic tumour; tumour, odontogenic; tumours, odontogenic; neoplasms, dental tissue; dental tissue neoplasms; dental tissue neoplasm; neoplasm, dental tissue; tissue neoplasm, dental; and tissue neoplasms, dental.

The free-text terms used were “odontogenic keratocyst” and “keratocystic odontogenic tumour”. These terms were also used to search LILACS. To include as many reports as possible the emphasis was placed on recall rather than precision, bearing in mind that the MeSH for dentistry and radiology is generally inadequate and that free-text searching may not hit the relevant article if the free-text term used was not included in the title or abstract. This strategy was further augmented by reference to the bibliographies (or citation lists) of all reports identified by the databases (reference harvesting) or hand-searching of journals listed in Table 1 of the SR on FocOD.⁹ Both database searches and hand-searches were last conducted on 2 September 2009.

The decision to include a report was generally made by reading the title and the abstract. As abstracts were used infrequently before 1979 it was anticipated that a call for the full paper, to determine whether it should be considered by the selection criteria, would be made more frequently for reports published before that year.

Strategy for sifting the literature

Selection criteria: There were three inclusion criteria (1 to 3) and three exclusion criteria (A to C) for the SR. Each report passed through these criteria in strict sequence. Although a report may be excluded by more than one criterion, only the first criterion to exclude a particular report was entered in the Appendix. For the sake of brevity only those reports which cannot be readily included by reference to their title or abstract will be discussed and cited.

Information included in the SR was generally reduced to numbers and tabulated. This took account of the number of cases that passed the selection criteria for inclusion and, therefore, may differ from the numbers available in the original report. Information not given (ING) was applied wherever information on a particular feature could not be determined (either expressed or implied) from the original text. Inadequate information given (IIG) was applied to features in a partially included report, which had been compromised and could not be included in the SR. IIG was entered against those features which the reporters had not adequately quantified.

The aim was not only to include as many reports as possible, but also as many features of those reports as possible, and to include as many cases of each report

Table 1 (a). Keratocystic odontogenic tumour: systematic review - analysis of the included reports

First author (year) [Language of publication] [Database]	National and/or ethnic origin	Period covered	No. of KCOT (No. KCOT per yr) [BCNS] {multi}	Gender		Age mean (range) in years Pre-presenting duration mean (range) in years	Presenting signs and symptoms			Site				Comments and number (%) of orthokeratotic type or variant Follow-up (FU) and recurrence
				Males	Females		Swelling	Pain	Other	Mandible		Maxilla		
										Ant.	Post.	Ant.	Post.	
Borello ((1976) ¹⁷ [Spanish] [MEDLINE;Me1, T ₁]	Argen- tinian	1957–1976 20 years	14*(0.7) [1,E]	11	3	36.7 SD 17.2 (12–72) ING	11	0	1 incid 4 pus 2 trismus 3 numb 3 Noerupt	0	14	0	0	*excludes 3 OKs (17.6%) FU mean 5.1(0.5–13)years: 1 recurs after 10 years
Mosadomi (1976) ¹⁸ [English] [MEDLINE:Me1&2 T ₁]	Nigeria	1969–1974 5 years	3 (0.6)	2	1	53.0 SD 22,9 (27–70) 2.1 SD 2.6 (0.25–5) ING	3	3	2 Pus	0	3	0	0	FU IIG; IIG recurred *excludes 30 OKs(11.8%), 22 P&OK and 50 recurrent cases FU ING; IIG recur *excludes 6 OKs (7.7%) & 9 P&OKs FU ING; ING recur *excludes 3 OKs (18.8%) & 1 P&OK FU IIG; IIG recurred *excludes 60 OKs (13.3%) FU ING; ING recur *excludes 2OKs (11.8%), 1 P&OK. 3 Inflamm FU ING; 1 recur twice *excludes 1 OK (4.5%) FU ING; ING recur
Brannon (1977) ^{19,20} [English] [MEDLINE:Me1, T ₁]	USA	1950–1972 22 years	224* (10.2) [16,E] {18,E}	ING		ING ING	ING	ING	ING		ING		ING	
Cohen (1980) ²¹ [English] [MEDLINE;Me, T ₁]	South African	ING	72*	ING		ING ING	ING	ING	ING		ING		ING	
Anniko (1981) ²² [English] [MEDLINE:Me1, T ₁]	Swedish	ING	13* [1,E] {2,E}	IIG		IIG ING	IIG	IIG	IIG		ING		ING	
Wright (1981) ²³ [English] [MEDLINE:Me1, T ₁]	USA	1950–1980 30 years	390* (13.0)	ING		ING ING	ING	ING	ING		ING		ING	
Chiang (1982) ²⁴ [English] [MEDLINE:Me1, T ₁]	Taiwanese	1959–1979 21 years	15 (0.8)	6	9	36.4 SD 21.7 ING	ING	ING	ING	3	8	1	3	
Balercia (1983) ²⁵ [Italian] [MEDLINE:Me1, T ₁]	Italian	1977–1983 7 years	21* (3.0)	ING		IIG ING	ING	ING	ING		IIG		IIG	

Table 1 (a) Continued

First author (year) [Language of publication] [Database]	National and/or ethnic origin	Period covered	No. of KCOT (No. KCOT per yr) [BCNS] {multi}	Gender		Age mean (range) in years	Presenting signs and symptoms			Site				Comments and number (%) of orthokeratotic type or variant Follow-up (FU) and recurrence	
				Males	Females		Pre-presenting duration mean (range) in years	Swelling	Pain	Other	Mandible		Maxilla		
											Ant.	Post.	Ant.		Post.
Geng (1983) ²⁶ [Chinese] [MEDLINE:Me, T ₁]	Chinese	1962–1980 19 years	88*(4.6)	IIG		IIG ING	IIG	IIG	IIG		IIG		IIG	*excludes 25 OK (22.1%) and 7 P&OK FU IIG;IIG recur	
Ahlfors (1984) ²⁷ [English] [MEDLINE:Me1, T ₁]	Swedish	1972–1982 11 years	244* (22.2) [5,I] {7.I}	160*	84*	41.0(8–83) ING	ING	ING	ING		IIG		IIG	*excludes 11 OKs (4.5%). FU ING; 69 (All PK) recurred after a mean of 5 yrs	
Blondeau (1986) ²⁸ [French] [MEDLINE;Me1, T ₁]	Canadian	9 years	67*(7.4) [3,E] {6,I}	IIG		IIG ING	ING	ING	ING		IIG		IIG	*excludes 1 OK (1.5%); FU IIG; IIG recur	
Chen (1986) ²⁹ [English] [MEDLINE;Me1, T ₁]	Taiwanese	1979–1983 5 years	12* (2.4)	IIG		IIG ING	ING	ING	ING		IIG		IIG	*excludes 2 OK (14.3%) and 2 P&OK FU ING; recur IIG	
Nielsen (1986) ³⁰ [French&German] [MEDLINE:Me1, T ₁]	Swiss	1979–1984 6 years	21* (3.5) [9,E]	12	9	(>9 to > 90) ING	IIG	IIG	7 insid	0 (17)	17	2	1	*includes 1P&OK FU 14: 0 recur	
Rodu (1987) ³¹ [English] [MEDLINE;Me1, T ₁]	USA (82W; 13B; 1E)	1976–1987 11 years	102 (9.3) [6,I]	55	47	28 median (9–77) M 9.7 yr >F ING	ING	ING	ING		72		28	FU IIG; 13 recur *includes 1 P&OK	
Haring (1988) ³² [English] [MEDLINE;Me1, T ₁]	USA	1982–1986 5 years	60* (15.0)	34	26	40.0 SD 19.4 (5–78) ING	16 out of 23	IIG	IIG		41		19	5 recur in 2–8 yrs	
Kakarantza- Angelopoulou (1990) ³³ [English] [MEDLINE;Me1]	Greek	1974–1986 13 years	57*(4.4) [7I]	IIG		IIG ING	ING	ING	ING		IIG		IIG	*excludes 2OKs (3.4%), 19 P&OKs and 9 recurrent cases FU ING; ING Recur	
Tagesen (1990) ³⁴ [Danish] [MEDLINE;Me1, T ₁]	Danish	1981–1989 8 years	27*(3.4)	IIG		IIG ING	ING	ING	ING		IIG		IIG	*excludes 5 recurrent cases FU IIG; IIG recur	

Table 1 (a) Continued

First author (year) [Language of publication] [Database]	National and/or ethnic origin	Period covered	No. of KCOT (No. KCOT per yr) [BCNS] {multi}	Gender		Age mean (range) in years Pre-presenting duration mean (range) in years	Presenting signs and symptoms			Site				Comments and number (%) of orthokeratotic type or variant Follow-up (FU) and recurrence
				Males	Females		Swelling	Pain	Other	Mandible		Maxilla		
										Ant.	Post.	Ant.	Post.	
Brøndum (1991) ³⁵ [English] [MEDLINE;Me1, T ₁]	Danish	1971–1983 13 years	27*(2.1)	14	13	IIG ING	ING	ING	ING		IIG		IIG	*excludes 5 OK (15.6%) 8 mands recur: 7 post 2 yrFU &1 post 5 yr FU
Crowley (1992) ³⁶ [English] [MEDLINE;Me1, T ₁]	USA (318W; 47B)	1970–1989 20 years	387* (19.4) [6,E]	236	145	39.6 ING	108 73 swell. & 35 expansion	58 ING	56 incid 8 numb 40 drain		269		114	*excludes 55 OK (12.4%) and 7 P&OK 113 recur out of 265 FU; recur mean 6.7 yr
Anand (1995) ³⁷ [English] [MEDLINE;Me1, T ₁]	USA	1977–1993 17 years	36* (2.2) [1,E] {1,I}		IIG	ING ING	ING	ING	ING		ING		ING	*lesions, excludes 21 OKs (36.2%) FU 14: 4 recur
Ong (1995) ³⁸ [English] [Reference-harvesting]	Malaysian (18C;8M; 9I)	1976–1992 17 years	24* (1.4) {4,E}		IIG	IIG ING	IIG	IIG	IIG		IIG		IIG	*excludes 3 OK (9.2%) and 6P&OK, 2 inflamed cysts FU IIG; IIG recur
el-Hajj (1996) ³⁹ [English] [MEDLINE;Me1&2, T ₁]	Swedish	1974–1993 20 years	41* (2.0) [2,E]		IIG	IIG ING	ING	ING	ING		IIG		IIG	*excludes 3 OK (6.8%) (0 recur) and 6 P&OK (2 recur) FU IIG; IIG recur
Filho (1997) ⁴⁰ [Portuguese] [LILACS]	Brazilian	1960–1994 35 years	39* (1.1)		IIG	IIG ING	ING	ING	ING		IIG		IIG	*excludes 15 OK (24.1%) FU IIG; IIG recur
Chow (1998) ⁴¹ [English] [MEDLINE;Me1, T ₁]	Singaporean (56C; 6M; 6I;2 other)	1981–1996 16 years	70* (4.4) [1,I]	44	26	32.8 (9–79) ING	36	13	11 incid 1Numb 11 pus	4 (48)	35	9 (19)	8	*76 cysts; excludes 6OKs (7.9%) FU mean 5 yrs: 7 recur All are PK
Francone (1999) ⁴² [Italian] [MEDLINE; Me1]	Italian	1985–1996 12 years	31* (2.6) [12,E]	19	12	42.0 (11–66) ING	ING	ING	ING	IIG (28)	IIG		3	FU 31: 7 recur once & 2 twice; 2 as amelo; 1 amelo became a SSCa

Table 1 (a) Continued

First author (year) [Language of publication] [Database]	National and/or ethnic origin	Period covered	No. of KCOT (No. KCOT per yr) [BCNS] {multi}	Gender		Age mean (range) in years	Presenting signs and symptoms			Site		Follow-up (FU) and recurrence		Comments and number (%) of orthokeratotic type or variant
				Males	Females		Swelling	Pain	Other	Mandible		Maxilla		
										Ant.	Post.	Ant.	Post.	
Santos (1999) ⁴³ [Portuguese] [LILACS]	Brazilian	1977–1998 22 years	47* (2.1) [1,E]	IIG		IIG ING	ING	ING	ING	IIG (41)	IIG	IIG (9)	IIG	*excludes 8 OKs (14.5%). Included P&OKs FU ING; ING Recur
Bolbaran (2000) ^{44,45} [English] [MEDLINE; T ₁]	Chilean	1975–1996 22 years	208* (9.4) [46,E]	IIG		IIG	IIG	IIG	IIG		IIG		IIG	*excludes 11 OKs (5.0%) and 4 P&OKs FU IIG; 40 recur
Kimi (2001) ⁴⁶ [English] [MEDLINE;Me1, T ₁]	Japanese	ING	24* [9,E]	14	10	IIG 44.8 sd 21.2 ING	ING	ING	ING		ING		ING	*excludes 10 recurrant all PK FU ING; ING Recur
Myoung (2001) ⁴⁷ [English] [MEDLINE;Me1, T ₁]	Korean	1980–1998 19 years	256* (13.5) [11,I] {39,I}	150	106	30.8 (>0 to < 70) ING	160	107	14 incid 17 discha 2 numb	35	131	29	35	*excludes 5 OKs (2.4%) 77 recur in 132 FU for mean 2.4 yrs; 9 had 2+recur
Stoelinga (2001) ⁴⁸ [English] [MEDLINE;Me1, T ₁]	Dutch	1973–1998 26 years	70* (2.7)	IIG		ING	IIG	IIG	IIG		IIG		IIG	*excludes 6 OKs (7.9%), 1P&OK and 5 recurrent cases FU IIG: IIG recur
Sortino (2002) ⁴⁹ [English] [MEDLINE;Me1]	Italian	1998–2000 3 years	12* (4.0)	IIG		ING IIG ING	ING	ING	ING		IIG		IIG	*excludes 3 OK (20.0%) FU IIG 0 recur
Monteiro (2005) ⁵⁰ [English] [LILACS]	Portuguese	1999–2001 3 years	10*(3.3) [3,E]	IIG		IIG ING	ING	ING	ING		IIG		IIG	*excludes 2 non PKs (16.7%) FU ING ; IIG recur
Chirapathom- sakul (2006) ⁵¹ [English] [MEDLINE; Me1, T ₁]	Thai	1988–2003 16 years	47*(2.9)	IIG		IIG IIG	IIG	IIG	IIG		IIG		IIG	*excludes 4 OKs (7.8%) FU IIG: IIG recur
Meningaud (2006) ⁵² [English] [MEDLINE;Me1]	French	1995–2005 10 years	87* (8.7) [8,E]	IIG		IIG ING	ING	ING	ING		IIG		IIG	*excludes 16 OKs (15.5%) & 21 P&OKs FU IIG: ING recur

Table 1 (a) Continued

First author (year) [Language of publication] [Database]	National and/or ethnic origin	Period covered	No. of KCOT (No. KCOT per yr) [BCNS] {multi}	Gender		Age mean (range) in years Pre-presenting duration mean (range) in years	Presenting signs and symptoms			Site		Comments and number (%) of orthokeratotic type or variant Follow-up (FU) and recurrence		
				Males	Females		Swelling	Pain	Other	Mandible		Maxilla		
										Ant.	Post.	Ant.	Post.	
Antunes (2007) ⁵³ [Portuguese] [LILACS]	Brazilian	1992–2007 15 years	69 (4.6) {5,I}	39	30	31.0(10–84) ING	20	IIG	49 incid		52		17	
Driemel (2007) ⁵⁴ [German] [MEDLINE;Me2,T ₂]	German	22 years	80* (3.6) {5,I#}		IIG	IIG	ING	ING	ING		IIG		IIG	FU ING; ING recur *excludes 6 treated elsewhere. #account for 12 cysts FU ING: IIG recur *excludes 9 OK (4.1%) FU ING; ING recur
Grossmann (2007) ⁵⁵ [English] [MEDLINE;Me1, T ₁]	Brazilian	1953–2003 51 years	208 (4.1) [8,I]	104	104	IIG IIG	ING	ING	ING		135		62	*GS accounts for extra cysts FU 32.5 (9–117) mth; 7 recur; Md > Mx
Habibi (2007) ⁵⁶ [English] [MEDLINE;Me2,T ₂]	Iranian (1H:1C)	1996–2006 10 years	74*(7.4) [6,I]	44	30	27.1 SD 3.7 (5–82) ING	50	11	20 incid 16 dischar	8*	48*	11*	16*	*gender and jaw not given for 1 and 11 FU ING; ING recur *Excludes 3 previous recur and 5 cases Nonspecific K FU ING; 2 recur in 2 yrs
Jing (2007) ⁵⁷ [English] [MEDLINE;Me2,T ₂]	Chinese	1952–2004 56 years	588* (10.5)	370	217	ING ING	ING	ING	ING	52	418	23	84	*excludes 1 with ameloblastoma 2 FU for 4 yrs; 1 recur * unreported number of OKs excluded FU ING; ING recur
Kolokythas (2007) ⁵⁸ [English] [MEDLINE;Me1, T ₁]	USA	1994–2004 10 years	14* (1.3) [3,E]	7	7	46.6 SD 15.9 ING	ING	ING	ING		9		5	
Ogunsalo (2007) ⁵⁹ [English] [MEDLINE;Me1, T ₁]	Jamaican	1980–1995 16 years	3 (0.2) [1,E]	1	2	33.3 SD 11.0 (21–44) ING	ING	ING	ING	0	3	0	0	
Ali (2008) ⁶⁰ [English] [MEDLINE;Me1, T ₁]	Kuwaiti	2004–2005 2 years	13* (6.5)	7	6	40.0 (6–62) ING	ING	ING	ING		2		11	

Table 1 (a) Continued

First author (year) [Language of publication] [Database]	National and/or ethnic origin	Period covered	No. of KCOT (No. KCOT per yr) [BCNS] {multi}	Gender		Age mean (range) in years	Presenting signs and symptoms			Site				Comments and number (%) of orthokeratotic type or variant Follow-up (FU) and recurrence	
				Males	Females		Pre-presenting duration mean (range) in years	Swelling	Pain	Other	Mandible		Maxilla		
											Ant.	Post.	Ant.		Post.
Gonzalez-Alva (2008) ⁶¹ [English] [MEDLINE;Me1,T ₂]	Japanese	1978–2006 28 years	183* (6.5) [11,I] {13,I}	94	89	32.8(6–78) ING	ING	ING	ING	8 (129)	97	4 (30)	10	*excludes 11 OOC (6.5%). includes 12 P&OK FU; 24 recur(all PK)	
Luo (2009) ⁶² [English] [MEDLINE;T ₂]	Chinese	1985–2006 22 years	507 (23.0) [22E]	323	184	36.0 SD 16.1 ING	ING	ING	ING	38 (345)	307	34 (117)	83	FU ING; ING recur	
Madras (2008) ⁶³ [English] [MEDLINE;Me1&2,T ₂]	Canadian	ING	16*	IIG		ING ING	ING	ING	ING	3	11	(6)	5	*excludes 5 treated elsewhere FU 0.2–7 yrs; 6 recur within 2 yrs(C)	
Yagyuu (2008) ⁶⁴ [English] [MEDLINE;Me2,T ₂]	Japanese	1981–2002 21 cases	75* (3.6)	49	25	41.1 (8–83) ING	IIG	IIG	21 incid	9 (55)	44	5 (20)	11	FU mean 40.3(0–183) month:7 recur (2 twice) mean 34(13–39 months)	
El-Gehani (2009) ⁶⁵ (English) [MEDLINE:T ₂]	Libyan	1997–2007 17 years	52 (3.0)	32	20	IIG ING	ING	ING	ING	4	31	6	11	FU ING; ING recur	
Gosau (2009) ⁶⁶ (English) [MEDLINE;T ₂]	German	1996–2006 10 years	34* (3.4)	21	13	40.9 ING	ING	ING	ING	2 (34)	32		2*	*2 cases with KCOT in each jaw. 11 recurred out of 22. 2 recurred out of 14	
MacDonald- Jankowski (2010) ⁶⁷ [English]	Hong Kong Chinese	1989–2004 16 years	33*(2.1) [6,E] {1,E}	18	15	30.3 SD 15.9 0.8 SD 1.3	20	12	6 incid 1 numb 5 pus	0 (20)	13	2 (13)	8	*excludes 6 OKs (15.0%) & 1 P&OK FU of 31 for a mean of 8.3 SD 4.6 years; 3 recur	

E, exclude; FU, follow-up; I, include; IIG, inadequate information given; ING, information not given; incid, incidental finding
Me1, MeSH “odontogenic cyst”; Me2, MeSH “odontogenic tumour” Number. Hosp/year, Number of cases per hospital per year
OK., orthokeratotic type; OR, orthokeratinized odontogenic cyst; PK, parakeratotic type; P&OK, mixed parakeratotic and orthokeratotic type
T₁, MEDLINE textword “Odontogenic keratocyst”; T₂, MEDLINE textword “Keratocystic odontogenic tumour”

Table 1 (b) Keratocyst odontogenic tumour: systematic review — mean number of features per SR-included OF reports in relation to global groups

Features	Global groups				
	All (number of reports)	East Asian (number of reports)	Sub-Saharan African (number of reports)	Latin American (number of reports)	Western (number of reports)
Number of cases	96.86 SD 131.47 (49)	147.85 SD 191.65 (13)	26.00 SD 38.84 (3)	97.50 SD 87.38 (6)	80.03 SD 105.80 (27)
Number of years	16.64 SD 11.12 (45)	21.33 SD 12.17 (12)	10.50 SD 7.78 (2)	25.83 SD 15.59 (6)	12.68 SD 7.37 (25)
Number of cases/year	5.84 SD 5.57 (45)	6.31 SD 6.47 (12)	0.04 SD 0.28 (2)	3.67 SD 3.22 (6)	6.54 SD 5.60 (25)
Age at first presentation	37.81 SD 6.33 (20)	35.62 SD 5.10 (8)	43.15 SD 13.93 (2)	33.85 SD 4.03 (2)	39.65 SD 5.54 (8)
<i>Statistical analysis: Student t-test:</i>					
Number of years: East Asian vs Western			$t = 2.27$; 35df: $0.05 > P > 0.01$		

as the selection criteria would allow. This required a separate strategy. Although the terms “exclusion”, “deletion” and “deduction” are normally synonyms, for the purposes of this SR they are specifically defined as follows: exclusion, the non-inclusion of a report in the SR and is used regardless of whether it is in relation to either inclusion or exclusion selection criteria; deletion, the removal of cases within a report that are not consistent with one or more of the selection criteria and have been reported in sufficient detail to permit their identification and removal from the report, therefore allowing the rest of the report to be included in the SR; deduction, is applied to those reports where deletion is not possible and the number of non-deletable cases exceeds 10% of the report (thus exceeds the “less than 10% allowance” for such non-conforming and non-deletable cases). For deduction to be permitted the report must include, for at least one feature, wholly inclusive words, such as “all” or “every” qualifying patient or case. “Almost all/every” or “the overwhelming majority”; for example, “... of the reported lesions were well-defined” were construed to be over 90% (or less than the 10% allowance) and as a result were considered to approximate to 100% and considered to be wholly inclusive. On the other hand studies reporting “most” or “majority” of the cases were well-defined were not admitted (for an example refer to the SR on fibrous dysplasia),⁷ because these and similar phrases are construed to represent 51–89% and, therefore, well outside the 10% allowance. The strategy for minimizing the impact of non-conforming reports on the SR was exclusion, deletion and deduction (including the less than 10% allowance rule).

Inclusion criteria: Criterion 1. Consistency with the WHO classification. The lesions had to be, at least, consistent with the histopathology established by the WHO’s 2005 edition of its classification of odontogenic tumours.² Although this described only the parakeratotic type as KCOT, it excluded the orthokeratotic type, or OOC, considering it a separate lesion. To include only data pertaining to KCOT it excluded reports if:

- (a) the details of their non-KCOT cases (that is all their orthokeratotic cases) could not be identified and deleted;

- (b) their unidentified cases in (a) exceeded the “less than 10 % allowance”. The whole report was excluded unless there remains at least one feature that clearly refers only to the parakeratinized variant (deduction). The report will be included only with regards to that particular feature.

It should be noted that although the mixed parakeratotic and orthokeratotic cases were not considered by the WHO’s 2005 edition,² they were not expressly excluded. It is reasonable to surmise the very presence of a parakeratotic element would merit their inclusion. Nevertheless, adequately identified mixed cases were removed. Their removal or retention is indicated in the comments column of Table 1.

Criterion 2. Non-syndromic cases. KCOT is a feature of NBCCS also known as Gorlin-Goltz syndrome.² Although there is no doubt that these lesions are KCOTs, they not only present earlier in life, but are also likely to recur after surgery.⁸ To enhance our understanding of the more common solitary form the following strategy was employed, it excludes reports if:

- (a) the details of their syndromic cases could not be identified and deleted;
- (b) their unidentified syndromic cases exceed the “less than 10% allowance”. The whole report was excluded unless there remained at least one feature that clearly refers only to non-syndromic or solitary KCOT (deduction). The report was only included with regard to that particular feature.

Criterion 3. A complete collection of KCOT cases. The study should represent a complete collection of cases of KCOT, arising within a particular community, occurring in the reporter’s caseload. Reports that were merely a selection of cases, such as case reports and those studies primarily concerned with specific investigations or a discrete age group, such as children or a particular jaw, were excluded.

Exclusion criteria: Criterion A. Excludes data already reported and included in the SR. It prevented double reporting of the same clinical cases, by excluding those

Table 1 (c) Keratocyst odontogenic tumour: systematic review — number of features per SR-included OF reports in relation to global groups

<i>Features</i>	<i>Global groups</i>				
	<i>All (number of reports)</i>	<i>East Asian (number of reports)</i>	<i>Sub-Saharan African (number of reports)</i>	<i>Latin American (number of reports)</i>	<i>Western (number of reports)</i>
Male: female	1866:1243 (26)	1068:681 (9)	3:3 (2)	154:137 (3)	641:422 (12)
Number of cases; swelling Y:N	316:226 (8)	216:143 (3)	3:0 (1)	31:52 (2)	66:31 (2)
Number of cases; pain Y:N	146:304 (6)	119:170 (2)	3:0 (1)	0:14 (1)	24:120 (2)
Number of cases; incidental findings Y:N	129:486 (9)	52:382 (4)	0:3 (1)	50:33 (2)	27:68 (2)
Number of cases; numb Y:N	7:366 (4)	4:355 (3)	ING	3:11 (1)	ING
Number of cases; discharge (pus) Y:N	55:395 (6)	33:326 (3)	2:1 (1)	4:10 (1)	16:58 (1)
Number of jaws; Mandible: maxilla	2059:797 (25)	1234:374 (8)	6:0 (2)	242:88 (4)	577:335 (11)
Number of sextants; Maxilla, Ant: Post	126:275 (12)	107:242 (8)	ING	ING	19:33 (4)
Number of sextants; Mandible, Ant: Post	166:1214 (16)	149:1053 (8)	0:6 (2)	0:14 (1)	17:141 (5)
Number of recurrent lesions post FU; Y:N	276:705 (15)	118:375 (5)	1:1 (1)	1:13 (1)	156:316 (8)
Number of orthokeratin: parakeratin.cases	332:2992 (29)	63:728 (9)	6:72 (1)	46:516 (5)	217:1676 (14)
Number of Exclud mixed: parakerat.cases	108:1391 (15)	17:172 (5)	9:72 (1)	4:208 (1)	78:939 (8)
Number of Includ.mixed:parakerat.cases	14:253 (3)	12: 172 (1)	ING	IIG:47 (1)	2:81 (2)
Number of syndrom.: non-syndrom. cases	199:2925 (27)	54:1074 (7)	1:2 (1)	56:468 (4)	88:1381 (15)

Entry in italics is not included in the analysis

Am, American; Exclud., excluded; Includ., included; Y:N; Yes:No; Ant:Post; Anterior:Posterior. ING, information not given; parakeratin; parakeratotic type of the odontogenic keratocyst or now simply the KCOT; orthokeratin; orthokeratotic type of the odontogenic keratocyst or now the Orthokeratinized odontogenic cyst; S-SAfrican, sub-Saharan African; syndrom; syndromatic cases, Gorlin-Goltz or “naevoid basal cell carcinoma syndrome”; post FU, after follow-up

Statistical analysis: χ^2

Male: female: East Asian vs Latin American	$\chi^2 = 6.87$: 1df: 0.01 > $P > 0.001$
Male: female: Latin American vs Western	$\chi^2 = 5.16$: 1df: 0.05 > $P > 0.01$
Swelling: Latin American vs Western	$\chi^2 = 16.89$: 1df: $P < 0.001$
Swelling: East Asian vs Latin American	$\chi^2 = 13.51$: 1df: $P < 0.001$
Pain: East Asian vs Western	$\chi^2 = 26.29$: 1df: $P < 0.001$
Incidental Finding: East Asian vs Western	$\chi^2 = 16.54$: 1df: $P < 0.001$
Incidental Finding: Latin American vs Western	$\chi^2 = 18.29$: 1df: $P < 0.001$
Incidental Finding: East Asian vs Latin American	$\chi^2 = 102.22$: 1df: $P < 0.001$
Discharge: East Asian vs Western	$\chi^2 = 9.39$: 1df: 0.01 > $P > 0.001$
Mandible: maxilla: East Asian vs Western	$\chi^2 = 46.11$: 1df: $P < 0.001$
Mandible: maxilla: Latin American vs Western	$\chi^2 = 10.95$: 1df: $P < 0.001$
Recurrence: East Asian vs Western	$\chi^2 = 12.67$: 1df: $P < 0.001$
Orthokeratin: parakeratin: East Asian vs Western	$\chi^2 = 13.23$: 1df: 0.01 > $P > 0.001$
Orthokeratin: parakeratin: Latin American vs Western	$\chi^2 = 4.86$: 1df: 0.05 > $P < 0.001$
Excluded Mixed cases: East Asian vs Latin American	$\chi^2 = 10.16$: 1df: $P < 0.01$
Excluded Mixed cases: sub-Saharan African vs Latin American	$\chi^2 = 11.72$: 1df: $P < 0.001$
Excluded Mixed cases: Latin American vs Western	$\chi^2 = 9.21$: 1df: 0.01 > $P > 0.001$
Syndrome: non-syndrome: East Asian vs Latin American	$\chi^2 = 20.02$: 1df: $P < 0.001$
Syndrome: non-syndrome: Latin American vs Western	$\chi^2 = 12.64$: 1df: $P < 0.001$

reports in which the data had already been reported and included in the SR, either by the same or different authors, unless the degree of overlap did not exceed 50% and there was at least one statistically significant different feature between them.

Criterion B. Excludes cases that recurred after primary treatment given elsewhere and/or earlier than the range in years of the study. It excludes reports if:

- (a) the details of their recurrent (recidivist) cases could not be identified and deleted;

- (b) their unidentified recurrent cases exceed the “less than 10% allowance” the whole report was excluded, unless there remains at least one feature that clearly refers only to the primary (never treated before) lesions (deduction), which are presenting for the first time. The report was only included with regards to that particular feature.

Criterion C. Excludes referred cases. It reinforces Criterion 3 by minimizing dilution of the data arising primarily within a specific community. It therefore excludes reports that include referred cases from

outside that community. This is because they may possess unusual features that may skew the profile of KCOT within that community, which would, in turn, skew the SR. To include only data pertaining to the jaws, it excluded reports if:

- (a) their referred cases could not be identified and excluded;
- (b) the unidentified referred cases exceed the "less than the 10% allowance." The whole report was excluded unless there remains at least one feature that clearly refers only to those cases arising within that community (deduction). The report was included only with regards to that particular feature.

Interpretation of the literature retrieved

Definition of parameters: Definitions of parameters, such as number of years a report covered, number of KCOTs per year, division of each jaw into sextants and radiologically apparent boundaries between the basal and alveolar processes for each jaw, are the same as the recent SR on FocOD.⁹

The term "radiolucency" could be implied from the reference to the radiological shape of lesions as unilocular or multilocular and these implied that the lesion was a radiolucency.

Global groups: In order to determine deeper patterns within the SR, the reports were divided into four global groups broadly based on ethnicity. These were East Asian (predominantly represented in this SR by Chinese and Japanese), sub-Saharan African (predominantly black African, including Jamaica), Western/Caucasian (North American and European (including Turkey), Middle Eastern, North African and Indian) and Latin American (including Cuba). Although the Western group was predominantly white (Caucasian, classically European and Middle Eastern) it contained significant non-white minorities, particularly from sub-Saharan Africa. The population of the USA was at the last census 69.1% white.¹⁰ Reports from the Indian sub-continent are included in the Western/Caucasian group, because 95% of Indians are Caucasian (Indo-Aryans and Dravidians). Although these four global groups are cartographically represented by four almost discrete regions, they are not primarily regional, because variable socio-economic and other ethno-cultural factors also play important roles that affect the availability and provision of diagnosis and treatment; for example, the South Asian nations, including India, although largely Caucasian, are still developing their economies, along with many of those in sub-Saharan Africa. Although Africa itself is divided between a Caucasian north and a substantially black sub-Saharan south, it is the latter which constitutes the bulk of the population of the African continent and the African diaspora (Jamaica is 90% of sub-Saharan African origin). Previous SRs have shown that nearly all SR-included African reports are from south of the Sahara.^{11–16} The important point of this global distribution is to determine the number, size

and quality of the SR-included reports to determine which communities are well reported and which are underreported.

Statistical analysis: Significant differences in frequencies were analysed using χ^2 test with $P < 0.05$. Significant differences in age were analysed using Student's *t*-test with $P < 0.05$.

Results

Systematic review

Many of the reports were automatically rejected because it was clear from reading the title or abstract that they were single case reports or review articles. Figure 1 outlines the process and disposal of the reports considered for a call of the full paper. Figure 1 includes all reports except reference 67 because the present author was a co-author, and the paper was already known to the present author/reviewer prior to conducting the SR.

Selection criteria

The 49 SR-included consecutive case series contained within the 51 reports^{17–67} are set out in Tables 1 – 4 and the 102 consecutive case series in 104 reports excluded under specific exclusion criteria are set out in the Appendix. It should be noted that, in order to be as clear as possible, when a case series rather than a specific report is intended then case series will be used. Although the source of the literature (MEDLINE, LILACS, reference-harvested or hand-searched) did not differ between the reports excluded or included, reports identified solely by LILACS and published before 1990 were significantly more likely to be excluded than those published on or after 1990 (Table 2). The Hong Kong report⁶⁷ was excluded from the analysis of the source in Table 2 because the present author was one of its co-authors.

The language of publication, when grouped into English, other European and East Asian languages, had no significant effect on inclusion.

Proportionally more Western/Caucasian reports were excluded from the SR than included; however, this was not significant. Western reports were significantly less likely to be excluded after 1990 whereas those from Latin America were significantly more likely to be excluded after 1990 (see Table 2).

82% of reports were first excluded under criterion 1. There was no significant difference regarding reports excluded under criterion 1 published prior to 1990 and those published on or after 1990 ($\chi^2 = 3.59$, 1 degree of freedom (df), $P > 0.05$).

Although not an exclusion criterion, the exclusion of the mixed (parakeratotic and orthokeratotic) cases occurred in 13 reports without further deduction of the details. This was largely owing to all the necessary deduction having been already undertaken to exclude the purely orthokeratotic (or OOC) cases, which was a fundamental exclusion criterion (criterion 1).

The MEDLINE search was as follows -

#1 Search "odontogenic cyst"[MeSH-Human] [Me1]	4143
#2 Search "odontogenic neoplasms"[MeSH-Human] [Me2]	4864
#3 Search "odontogenic keratocyst"[freetext-Human] [T1]	4369
#4 Search "keratocystic odontogenic tumour", [Text-Word][T2]	39
#5 Search (#1) or (#2) or (#3)→5199 titles→168 full papers→→→→→139 called-up & reviewed	1

The LILACS search was as follows -

Reference Harvesting of those

"odontogenic cyst"	48
"odontogenic cysts"	92
"keratocystic odontogenic tumour"	1
Total → full paper called-up & reviewed→→→→→→→→→→→9	1

HANDSEARCHING of journals (see Table 1 of Reference 12)→→→→→0→1

1→148→REFERENCE-152→ SELECTION →50 SR-included reports of 48 case series*
HARVESTING CRITERIA

SOURCES of	SR-included reports	SR-excluded reports
MEDLINE	45#	94
LILACS	4	5
Handsearching	0	0
Reference harvesting	1	3

* Does not include Reference 67, for which the present author was a co-author
number includes 2 sets of reports each reporting the same case series

Figure 1 Keratocystic odontogenic tumour: systematic review - search strategy and results

Analysis of the SR

49 series of consecutive cases, in 51 reports (2 communities were each represented by 2 reports), were included in the SR (Table 1).¹⁷⁻⁶⁷ The clinical features decades, age distribution in decades at first presentation and radiological details extracted from each of the series are shown in Tables 1, 3 and 4, respectively.

The MeSH "odontogenic tumour" and/or the MEDLINE textword "keratocystic odontogenic tumour" were more effective at recalling KCOT reports from 2007 onwards, whereas the MeSH "odontogenic cyst" and MEDLINE textword "odontogenic keratocyst" were, until 2007, extremely effective in recalling KCOT reports; however, they displayed a marked reduction in effectiveness after that year.

Although all four global groups were represented, the sub-Saharan African group was only represented in

three reports. Just under half of the reports were derived from the Western group. Reports from the East Asian group were derived from a wide range of nations. The mean range in years covered by the East Asian reports was significantly larger than that of the Western reports.

The number of KCOTs per year is shown in Table 1a; however, this was not determinable for four reports. The number of KCOTs per year fell from 7.68 (SD 6.57) KCOTs per year in the 12 series of cases reported prior to 1990, to 5.17 (SD 5.13) KCOTs per year in the 33 series of cases reported after and including 1990; this was not significant ($t = 1.20$, 43 df, $P > 0.05$).

Although the mean number of cases ranged widely between the global groups (Table 1b), this was not significant.

Most case series originally included the patients' ethnic origin, sex, age, site affected and presenting

Table 2 Keratocyst odontogenic tumour: systematic review: comparison between SR-included and SR-excluded reports

Source of reports	MEDLINE	LILACS	Reference-harvesting	Handsearching
SR-included reports/SR-excluded reports	45 of 50/94 of 102	4 of 50/5 of 102	1 of 50/3 of 102	0 of 50/0 of 102
Source-SR-excluded reports	MEDLINE	LILACS	Reference-harvesting	Handsearching
SR-excluded: on or after1990/before 1990	45 of 52/49 of 50	5 of 52/0 of 50	2 of 52/1 of 50	0 of 52/0 of 50
Language of publication	English	Other European	East Asian	
SR-included reports/SR-excluded reports	39 of 50/74 of 102	10 of 50/23 of 102	1 of 50/5 of 102	
Language of publication-SR-excluded reports	English	Other European	East Asian	
SR-excluded: on or after1990/before 1990	42 of 52/32 of 50	8 of 52/15 of 50	2 of 52/3 of 50	
Global groups	East Asian	Sub-Saharan	Latin American	Western
SR-included reports/SR-excluded reports	12 of 50/20 of 102	3 of 50/2 of 102	6 of 50/11 of 102	27 of 50/70 of 102
Global groups-SR-excluded reports	East Asian	Sub-Saharan	Latin American	Western
SR-excluded: on or after1990/before 1990	14 of 52/6 of 50	1 of 52/1 of 50	10 of 52/1 of 50	27 of 52/42 of 50
Statistical analysis: χ^2 :				
Source-SR-excluded reports: SR-excluded: on or after1990/before 1990: LILACS	$\chi^2 = 5.26$ 1df: $0.05 > P > 0.01$			
Global groups-SR-excluded reports: SR-excluded: on or after1990/before 1990: Western	$\chi^2 = 12.05$ 1df: $P < 0.001$			
Global groups-SR-excluded reports: SR-excluded: on or after1990/before 1990: Latin American	$\chi^2 = 7.89$ 1df: $0.01 > P > 0.001$			

Table 3 Keratocyst odontogenic tumour: systematic review - distribution of cases according to age (in decades). The number of males and females are in parentheses

Report (ref) [global group]	Borello ¹⁷	Mosa- domi ¹⁸	Chiang ²⁴	Neilson ³⁰	Ha- ring ³²	Brondum ³⁵	Chow ⁴¹	Myoung ⁴⁷	Antunes ⁵³	Gross- man ⁵⁵	Habibi ⁵⁶	Jing ⁵⁷	Ogun- salo ⁵⁹	Gonzales- Alva ⁶¹	Luo ⁶²	El- Ge- hani ⁶⁵	Mac- Donald- Jan- kowski ⁶⁷	Total for each decade	Decade percnt; of total	% of males/ decade
Decade	[L]	[A]	[E]	[W]	[W]	[W]	[E]	[E]	[L]	[L]	[W]	[E]	[A]	[L]	[E]	[W]	[E]			
0-9	0	0	0	3(0:3)	4	1(0:1)	1	11(6:5)	2	4	4	3	0	3(1:2)	3	1	0	40(7:11)	1.9	38.9
10-19	2(1:1)	0	3(3:0)	7(5:2)	7	5(1:4)	14	64(39:25)	14	46	21	80	0	45(23:22)	70	10	9(6:3)	397(78:57)	18.9	57.8
20-29	5(4:1)	1(1:0)	5(1:4)	3(1:2)	18	8(2:6)	21	74(38:36)	23	64	15	169	1(1:0)	53(26:27)	113	22	14(6:8)	610(80:84)	29.0	48.8
30-39	1(1:0)	0	0	2(2:0)	6	4(0:4)	11	40(24:16)	15	31	9	141	1(0:1)	24(13:11)	105	6	1(1:0)	397(41:32)	18.9	56.2
40-49	1(1:0)	1(1:0)	2(1:1)	1(0:1)	6	10(6:4)	11	34(22:12)	9	25	7	82	1(0:1)	16(8:8)	74	2	4(2:2)	286(41:29)	13.6	58.6
50-59	2(1:1)	0	1(0:1)	2(2:0)	7	7(4:3)	9	21(13:8)	3	10	6	57	0	17(10:7)	45	5	2(2:0)	194(32:20)	9.2	57.7
60-69	0	0	2(1:1)	1(1:0)	12	3(2:1)	2	12(8:4)	2	2	1	46	0	15(8:7)	37	0	2(0:2)	137(20:15)	6.5	57.1
70-79	1(1:0)	1(0:1)	2(0:2)	1(0:1)	2	5(2:3)	1	0	1	8	0	8	0	7(4:3)	IIIG*	0	1(1:0)	38(8:10)	1.8	44.4
80-89	0	0	0	0	0	0	0	0	0	0	1	2	0	0	IIIG*	0	0	3(0:0)	0.1	0
90-100	0	0	0	0	0	0	0	0	0	0	0	0	0	0	IIIG*	0	0	0(0:0)	0.0	0
Total	12 (9:3)	3(2:1)	15(6:9)	20 (11:9)	62	43(17:26)	70	256(150:106)	69	190	64	588	3(1:2)	180 (93:87)	447*	46	33(18:15)	2101 (307:255)	99.9	54.8

*15 cases occurred in patient 70 years of age and above, these were deducted from the original total of 462. A, sub-Saharan African; E, East Asian; L, Latin American; W, Western

Table 3 (Continued)

Report (ref) [global group] Decade	Western (5 reports)			East Asian (6 reports)			Latin American (4 reports)			Sub-Saharan African (2 reports)	
	Total for each decade	Decade % of total	% of males/ decade	Total for each decade	Decade % of total	% of males/ decade	Total for each decade	Decade % of total	% of males/ decade		
0-9	13(0:4)	5.5	0	18(6:5)	1.3	50.0	9(1:2)	2.0	33.3	0	
10-19	50(6:6)	21.3	50.0	240(48:28)	17.0	58.7	107(24:23)	23.7	51.1	0	
20-29	66(3:8)	28.1	27.3	396(45:48)	28.1	48.4	145(30:28)	32.2	51.7	2(2:0)	
30-39	27(2:4)	11.5	33.3	298(25:16)	21.1	57.6	71(14:11)	15.7	56.0	1(0:1)	
40-49	26(6:5)	11.1	54.5	207(25:15)	14.7	58.9	51(9:8)	11.3	81.8	2(1:1)	
50-59	27(6:3)	11.5	66.7	135(15:9)	9.6	61.0	32(11:8)	7.1	57.9	0	
60-69	17(3:1)	7.2	75.0	101(9:7)	7.2	54.8	19(8:7)	4.2	53.3	0	
70-79	8(2:4)	3.4	33.3	12(1:2)	0.8	50.0	17(5:3)	3.8	62.5	1(0:1)	
80-89	1(0:0)	0.2	0	2(0:0)	0.1	0	0	0	0	0	
90-100	0(0:0)	0.0	0	0	0	0	0	0	0	0	
Total	235(28:35)	99.8	44.4	1409 (174:130) (45:49)	100.0	57.2	451 (102:90)	100.0	53.1	6(3:3)	

Table 4 (a). Keratocyst odontogenic tumour: systematic review — analysis of the radiology in the included reports

Radiological features	Number	Shape							Expansion												Associated with unerupted tooth?	
		Complete radiolucent?		Unilocular		Multi-locular	Degree of marginal definition		Cortication or sclerosis of the periphery		Buccolingual		Lower border of the mandible displaced (and/or eroded)		Antral involvement		Tooth displacement		Root resorption			
		Yes	No	Smooth	Wavy		Well-defined	Poorly-defined													Yes	No
Author (year)		Yes	No	Smooth	Wavy		Well-defined	Poorly-defined	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Borello (1976) ¹⁷	14	12	0	5	1	6	IIG	IIG	ING	ING	2	12	IIG	IIG	N/A	N/A	IIG	IIG	ING	ING	ING	ING
Mosadomi (1976) ¹⁸	2	2	0	0		2	IIG	IIG	IIG	IIG	ING	ING	IIG	IIG	N/A	N/A	ING	ING	ING	ING	ING	ING
Chiang (1982) ²⁴	15	15	0	10		4	ING	ING	ING	ING	ING	ING	ING	ING	ING	ING	ING	ING	IIG	IIG	7	7
Nielsen (1986) ³⁰	21	ING	ING	10	7	4	ING	ING	IIG	IIG	ING	ING	ING	ING	ING	ING	ING	ING	IIG	IIG	IIG	IIG
Haring (1988) ³²	60	60	0	44		16	27	33	7	20	ING	ING	ING	ING	ING	ING	ING	ING	3	35	16	38
Tagesen (1990) ³⁴	38	38	0	28	6	4	ING	ING	ING	ING	ING	ING	ING	ING	ING	ING	ING	ING	ING	ING	ING	ING
Crowley (1992) ³⁶	387	256	0	ING	ING	ING	ING	ING	ING	ING	ING	ING	ING	ING	ING	ING	ING	ING	ING	ING	100	109
Santos (1999) ⁴³	40	50	0	41		9	ING	ING	ING	ING	ING	ING	ING	ING	ING	ING	ING	ING	ING	ING	10	50
Myoung (2001) ⁴⁷	256	ING	ING	ING	ING	ING	ING	ING	ING	ING	ING	ING	ING	ING	ING	ING	ING	ING	ING	ING	70	186
Ogunsalo (2007) ⁵⁹	3	3	0	ING	ING	ING	ING	ING	IIG	IIG	ING	ING	ING	ING	ING	ING	ING	ING	ING	ING	IIG	IIG
Yagyuu (2008) ⁶⁴	62	62	0	43		19	ING	ING	ING	ING	ING	ING	ING	ING	ING	ING	ING	ING	ING	ING	16	43
MacDonald-Jankowski (2008) ⁶⁷	33	33	0	16	0	17	33	0	29	4	27	6	10	4	11	0	22	10	13	19	20	12
Total	942	532	0	59	14	81	60	33	36	24	29	18	10	4	11	0	22	10	16	54	239	435
				211																		
Percentage		100	0	73		27	64	36	60	40	62	38	71	29	100	0	69	31	23	77	35	65

Table 4 (b) Keratocyst odontogenic tumour: systematic review — number of radiological features per SR-included OF reports in relation to global groups

Features	Global groups				
	All (number of reports)	East Asian (Number of reports)	Sub-Saharan African (Number of reports)	Latin American (Number of reports)	Western (Number of reports)
Shape: unilocular: multilocular	211: 81 (9)	69: 40 (3)	0:2 (1)	47: 15 (2)	95: 24 (3)
Degree of margin definition: good: poor	60: 33 (2)	33: 0 (1)	ING	ING	27: 33 (1)
Cortication: yes:no	36: 24 (2)	29: 4 (1)	ING	ING	7: 20 (1)
Buccolingual expansion: yes:no	29: 18 (2)	27: 6 (1)	ING	2: 12 (1)	ING
Root resorption: yes:no	6: 64 (2)	13: 19 (1)	ING	ING	3: 35 (1)
Associated unerupted tooth?: yes:no	237:437 (7)	111:250 (4)	ING	10: 40 (1)	116:147 (2)
ING, information not given					
<i>Statistical analysis: χ^2</i>					
Shape: unilocular:multilocular: East Asian vs Western	$\chi^2 = 7.70$: 1df: $0.01 > P > 0.001$				
Degree of margin definition: good: poor: East Asian vs Western	$\chi^2 = 28.01$:1df: $P < 0.001$				
Cortication?: yes:no: East Asian vs Western	$\chi^2 = 23.07$:1df: $P < 0.001$				
Buccolingual expansion?: yes:no: East Asian vs Latin American	$\chi^2 = 18.83$:1df: $P < 0.001$				
Associated unerupted tooth: yes:no: East Asian vs Western	$\chi^2 = 10.75$:1df: $P < 0.001$				
Associated unerupted tooth: yes:no: Latin American vs Western	$\chi^2 = 10.10$:1df: $P < 0.001$				
Root resorption: yes:no: East Asian vs Western	$\chi^2 = 10.43$:1df: $P < 0.001$				

clinical features; however, these could not be included in the SR. The extent of the deletions is evident from the distribution of IIG in Table 1a. Six SR-included reports exhibited widespread deletion.

Only two reports, one sub-Saharan African¹⁸ and the other East Asian⁶⁷, indicated the duration of the patients' pre-existing awareness of their lesions prior to first presentation. Although the period between first awareness of the lesion and first presentation for the east Asian report⁶⁷ was shorter than that for the sub-Saharan African, report it was not significant; $t = 0.87$: 27df: $P < 0.05$.

Males predominated in the East Asian, Latin American and Western global groups, but this was significantly lower for the Latin American group (Table 1c). The mean age at first presentation was higher for the Western global group than for the other three global groups; this was not significant (Table 1b). Table 3 is a comparison between 17 reports of the distribution according to age in decades. KCOTs first present most frequently in the third decade overall, and for the East Asian, Latin American and Western global groups. Females predominate in the first decade, while males predominated slightly from the second to the seventh decades.

Swelling and pain at first presentation were significantly more frequent in East Asians, whereas KCOT discovered as an incidental finding was more frequent in the Latin American reports (Table 1c). Numbness was the greatest proportionally for the sole small Latin American report.¹⁷ Cases presenting with numbness were also quantified in three East Asian reports.^{41,47,67}

Location of the lesions by quadrant or sextant was specified in only 15 case series for the mandible and 13 for the maxilla, whereas location by jaw was specified in 25 (Table 1c). The mandible was affected twice as frequently as the maxilla and significantly more for the

East Asian (77%) and Latin American (73%) compared with the Western global group (63%). There was no difference between the groups for either the mandibular or maxillary sextants; all four global groups display a predilection for the posterior sextants of both jaws.

Table 4a shows the radiological features and contains 12 SR-included reports covering four global groups; the sub-Saharan African group was represented by only two small reports. The general paucity of radiological detail is illustrated by the frequent use of ING. There was a significant predilection for a multilocular shape (Table 4b) in the East Asian global group (36.7%), in contrast with the Latin American (24.2 %) and Western (20.2 %) global groups.

64% of KCOTs were well-defined. One East Asian report (Hong Kong Chinese)⁶⁷ displayed significantly better marginal definition, cortication and buccolingual expansion than those from a Western report.³² Cortication occurred in 60% cases synthesized from these two reports. Only one report⁶⁷ revealed downward displacement or erosion of the lower border of the mandible (71%), involvement of the maxillary antrum (100%) and tooth displacement (32%). Root resorption occurred in 23% of a synthesis of two reports.^{32,67} A significant association with unerupted teeth occurred more frequently in the Western global group.

The overall recurrence rate was 28%. The recurrence rate was significantly higher in the Western global group (33%) compared with the East Asian global group (24%), which also synthesized a similar number of cases (Table 1c).

The number of the orthokeratotic type (or OOC), when compared with the number of the parakeratotic type (now KCOT) accounted for 10% of the combined OOCs and KCOTs overall. The proportion of OOCs was significantly greater for the Western global

group than for the East Asian and Latin American groups, which also included more than one case series (Table 1c). For the Western, East Asian, Latin American and sub-Saharan African global groups the proportion was 11%, 8%, 8% and 7%, respectively.

13 case series permitted the exclusion of mixed cases and 3 did not. The Latin American global group contained proportionately significantly fewer excludable mixed cases (2%) than the other global groups (East Asians, 9%; sub-Saharan Africans, 11%; and Western, 8% (Table 1c)). The overall percentage of mixed cases excluded and included in the SR were 7% and 5% respectively.

The percentage of syndromic cases for the East Asian, Latin American and Western global groups, containing more than one case series, were 6%, 11% and 6% respectively; the higher predilection for syndromic cases in the Latin American global group was significant (Table 1c). The overall mean was 7%.

Discussion

According to Madras and Lapoint⁶³ three factors led to the recharacterization of the keratocyst as KCOT. The KCOT exhibits locally destructive and highly recurrent behaviour; the histopathology of the KCOT reveals budding of the basal layer into the connective tissue and frequent mitotic figures; and, finally, the KCOTs are associated with an inactivation of PCHT, the tumour suppressor gene. The presence of a genetic component suggests that the patient's ethnic origin, which is "family history" written large, may have a role to play. The significant differences observed between the global groups in this SR suggest that ethnic origin of the KCOT patient is important.

The effectiveness of MEDLINE searches using MeSH and freetexting have reflected both the change in nomenclature of the parakeratinized type of odontogenic keratocyst to KCOT and its reclassification from cyst to neoplasm. Therefore, the most effective MeSH for searching for KCOT is now "odontogenic tumour" and the most effective textword is "keratocystic odontogenic tumour". Latin American reports, identified by LILACS, were published significantly more frequently after 1990. This is due, most likely, to the recent origin of this database and its widespread application to the Latin American literature.

The significantly greater range in years of the East Asian reports compared with the Western reports may reflect their earlier commencement of record keeping of this particular lesion.

The paucity of reports on KCOT from the sub-Saharan African global group stood in marked contrast to the SR of the ameloblastoma, another odontogenic lesion.^{11,12} There were only three small reports: Nigerian,¹⁸ South African (of undisclosed ethnic origin)²¹ and Jamaican.⁵⁹ Mosadomi¹⁸ reported that only 3 KCOTs presented in his Nigerian community over 5 years, whereas 19 ameloblastomas

presented during the same time-period. Furthermore, Rachanis and Shear⁶⁸ remarked on the lower frequency of keratocysts (this report was excluded under criterion 1 because the type of keratinization was not identified) affecting the South African black community in comparison with the white South Africans, the reverse was true for ameloblastoma. This would indicate that KCOTs occurred less frequently than ameloblastomas in at least two sub-Saharan African communities. This may explain why the three KCOTs in the Mosadomi¹⁸ report had been provisionally diagnosed as ameloblastomas.

It was clear from the significant proportion of OOC (or orthokeratotic type of the former odontogenic keratocyst) in the SR-included reports that they could have played a major role in the variability of outcomes in many reports, which did not distinguish between the types of keratinization. Such reports accounted for the vast majority of the SR-excluded reports. This reinforces the prior decision to deduct completely all features that would have also included OOC.

The removal of OOC cases, and those which are part of the NBCCS, was necessary because they are completely different lesions. The additional removal, whenever possible, of the mixed cases was desirable because they appear to be intermediate in behaviour between the KCOT and OOC. Although Crowley et al³⁶ compared the recurrence rates of KCOT (42.6%), OOC (2.2%) and mixed cases (14.3%), the mixed cases were few in number. Nevertheless, the separate evaluation of the clinical, radiological presentations and treatment outcomes of these mixed cases should be considered in future reports.

Although the frequency of mixed cases was highest in the sole sub-Saharan African report²¹ and lowest in the sole Latin American report^{44,45} detailing this feature, this phenomenon may not survive the addition of subsequent additional reports to these global groups.

There was no significant difference between reports included and excluded from the SR on the basis of membership of a particular global group, language of publication and source. This indicated that any bias against the inclusion of reports on the basis of global group, language of publication and source is unlikely.

Although the East Asian global group presented with significantly more pain and swelling, this was not reflected in significantly more cases presenting with a purulent discharge at first presentation. This may be due to two possibilities: the reporters of this global group did not report such a discharge or KCOT in East Asians is more likely to provoke swelling and pain. The Hong Kong Chinese presented their KCOTs at a young age.⁶⁷ Only Iranians in the report by Habibi et al⁵⁶ were younger. This was supported by a South Korean report by Myoung et al,⁴⁷ which reported a westernized East Asian community whose KCOTs presented at a young mean age of 31 years. Only 5% of the cases were discovered as incidental findings. These may suggest that in certain East Asian communities KCOTs first present with symptoms. The cause of such symptoms needs to be

considered; it is possibly not due to size or at least size alone. The largest report by Myoung et al⁴⁷ reported that each lesion affected a discrete sextant, either an anterior or a posterior sextant, but not both; therefore, the lesions were not unduly large. Nevertheless, KCOTs in one East Asian report (Hong Kong)⁶⁷ were significantly associated with buccolingual expansion when compared with one small Latin American report.¹⁷

KCOT in Latin Americans presented significantly more frequently with a discharge and numbness. They presented more frequently in the mandible and in its posterior sextant, where purulent infection of the KCOT can affect the inferior dental nerve and cause numbness.

Philipsen recently stated that root resorption was a rarity in KCOT.² Two SR-included reports, one each from the Western³² and East Asian⁶⁷ global groups, reported root resorption in 8% and 41% of the cases, respectively. Therefore, although root resorption is not common, it may not be rare in certain communities.

Although all global groups displayed a predilection for the mandible and for the posterior sextants of both jaws, the Western global group's significant association with unerupted third molars was unexpected, particularly as the largest of the two Western reports was an American report.³⁶ An explanation is that the KCOTs in this report may not have been affected by the purportedly high incidence of routine prophylactic removal of third molars in this community.

All global groups displayed recurrence, which on average occurred in one out of every four KCOTs removed; however, this may be an underestimate as follow-up may have not been carried out for a long enough period. Long-term follow-up is required for KCOT as Stoelinga⁴⁸ found that 5 cases recurred 6 to 25 years after enucleation. Recurrence in recent reports may be due to the type of treatment, for example decompression (marsupialization) may result in recurrence within 2 years. Pogrel⁶⁹ now suggests that decompression should be supplemented, once the cavity has been sufficiently reduced in size, by aggressive curettage and treatment with liquid nitrogen. Madras and LaPoint⁶³ state that the "WHO's reclassification ... underscores the aggressive nature of the lesion and should motivate clinicians to manage the disease in a correspondingly aggressive manner."

Conclusions

1. The global group, language of publication and source had no significant effect on whether a report was included or excluded from the SR.
2. The recent change in nomenclature and classification of the KCOT is already profoundly affecting the

effectiveness of the older search terms. This is also likely to be the case for other odontogenic lesions, which underwent a change in nomenclature and classification at the same time.

3. The inclusion of LILACS identified the majority of SR-included Latin American case series.
4. Many recent reports have not fully recognized that the OOC (formerly the orthokeratotic type of the odontogenic keratocyst) is a completely separate lesion and should be completely excluded from a report on KCOTs.
5. Those KCOTs associated with naevoid basal cell carcinoma syndrome displayed different characteristics from the non-syndromic cases and should either be reported separately or at least differentiated from the latter in a report.
6. In addition to OOC and NBCCS cases, the reporter should consider mixed cases separately regarding not only the clinical and radiological presentations, but also the treatment outcomes.
7. KCOT displayed differences between global groups and, therefore, the ethnic origin of the patient is important. Those of East Asian origin may present symptoms early, whereas KCOT in a Western community may be found as an incidental finding at a later stage. This places the onus on the patient to maintain regular check-ups and his or her dentist to review any radiographs fully. This should not be misread as an authority to radiologically screen the patient for an as yet undetected and symptomless disease, but if radiographs have been already taken for a clinically indicated reason then full use should be made of them to consider as yet undetected disease.
8. Three of the four global groups were well represented. The exception was the sub-Saharan Africa global group. Although only three small reports were included in the SR, it is clear that the incidence of KCOTs in this group is much lower than that of ameloblastomas.
9. It is clear from the frequency of ING, particularly in Table 4, that 12 out of the 49 SR-included case series reported little radiology beyond the fact that the KCOT is a radiolucency that presents with a unilocular or multilocular shape, and may be associated with unerupted teeth.
10. It would be valuable to determine whether there are any clinical and radiological features that could suggest an increased risk of recurrence.

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Appendix

Keratocystic Odontogenic Tumour: Excluded reports

Selection criterion	Report (First author's surname and date of publication)	Global group	Language of publication	Database
3	Avelar et al (2008) ⁷⁰	L	English	Me
3	Cavalcante et al (2008) ⁷¹	L	English	Me
3	González Moles et al (2008) ⁷²	W	English	Me
3	Kuroyanagi et al (2008) ⁷³	E	English	Me
1	Tortorici et al (2008) ⁷⁴	W	English	Me
1	Ochsensus et al (2007) ⁷⁵	W	English	Me
1	Jones et al (2006) ⁷⁶	W	English	Me
1	Maurette et al (2006) ⁷⁷	W	English	Me
1	Varinauskas et al (2006) ⁷⁸	W	English	Me
1	Bornstein et al (2005) ⁷⁹	W	French, German	Me
1	Camisasca et al (2005) ⁸⁰	L	Portuguese	Li
1	Kim et al (2005) ⁸¹	E	English	Me
3	Morgan et al (2005) ⁸²	W	English	Me
1	Bataineh et al (2004) ⁸³	W	English	Me
1	Koseoglu et al (2004) ⁸⁴	W	English	Me
1	Pippi & Vitolo (2004) ⁸⁵	W	English	Me

Appendix Continued

<i>Selection criterion</i>	<i>Report (First author's surname and date of publication)</i>	<i>Global group</i>	<i>Language of publication</i>	<i>Database</i>
3	Pogrel & Jordan (2004) ⁶⁹	W	English	Me
1	Vallejos & Briend (2004) ⁸⁶	W	Spanish	Li
1	Ali & Baughmann (2003) ⁸⁷	W	English	Me
1	de Amorim et al (2003) ⁸⁸	L	Portuguese	Li
A	Li et al (2003) ⁸⁹	E	Chinese	Me
1	Barreto et al (2002) ⁹⁰	L	English	Me
1	da Silva et al (2002) ⁹¹	L	English	Me
1	Nakamura et al (2002) ⁹²	E	English	Me
1	Tsukamoto et al (2002) ⁹³	E	English	Me
1	Zhao et al (2002) ⁹⁴	E	English	Me
1	Giardina et al (2001) ⁹⁵	W	English	Me
B	Schmidt & Pogrel (2001) ⁹⁶	W	English	R
1	August et al (2000) ⁹⁷	W	English	Me
1	Cabral et al (2000) ⁹⁸	L	Portuguese	Li
1	Chiapasco et al (2000) ⁹⁹	W	English	Me
3	de Paula et al (2000) ¹⁰⁰	L	English	Me
A	Lam & Chan (2000) ¹⁰¹	E	English	Me
1	Ledesma-Montes et al (2000) ¹⁰²	L	English	Me
A	Ngeow et al (2000) ¹⁰³	E	English	Me
1	Oda et al (2000) ¹⁰⁴	W	English	Me
1	de Quadros & Oliveira Calvet(2000) ¹⁰⁵	L	Portuguese	Li
1	Soost et al (1999) ¹⁰⁶	W	German	Me
1	Tay (1999) ¹⁰⁷	E	English	Me
1	Arotiba et al (1998) ¹⁰⁸	A	English	Me
1	Meara et al (1998) ¹⁰⁹	W	English	Me
1	Dammer et al (1997) ¹¹⁰	W	English	Me
3	Marker et al (1996) ¹¹¹	W	English	Me
1	Minami et al (1996) ¹¹²	E	English	Me
3	Nakamura et al (1995) ¹¹³	E	English	Me
1	Ikeshima (1995) ¹¹⁴	E	English	Me
1	Daley et al (1994) ¹¹⁵	W	English	Me
1	Das et al (1994) ¹¹⁶	W	English	Me
2	Berrone et al (1994) ¹¹⁷	W	Italian	Me
1	Kreidler et al (1993) ¹¹⁸	W	English	Me
1	Boon (1990) ¹¹⁹	E	English	R
1	Utsumi et al (1990) ¹²⁰	E	Japanese	Me
1	Gerlach et al (1989) ¹²¹	W	German	Me
3	Dominguez & Keszler (1988) ¹²²	L	English	Me
B	Jensen et al (1988) ¹²³	W	English	Me
1	Köndell & Wiberg (1988) ¹²⁴	W	English	Me
A	Stoelinga & Bronkhorst (1988) ¹²⁵	W	English	Me
1	Forssell et al (1988) ¹²⁶	W	English	Me
1	Kalusokoma et al (1987) ¹²⁷	W	French	Me
1	Partridge & Towers (1987) ¹²⁸	W	English	Me
1	Weir et al (1987) ¹²⁹	W	English	R
1	Woolgar et al (1987) ¹³⁰	W	English	Me
1	Gáspár et al (1986) ¹³¹	W	Hungarian	Me
A	Siar et al (1988) ¹³²	E	English	Me
1	Donath (1985) ¹³³	W	German	Me
1	Ewers & Härle (1985) ¹³⁴	W	German	Me
1	Hoffmeister & Harle (1985) ¹³⁵	W	German	Me
1	Lai & Chen (1985) ¹³⁶	E	Chinese	Me
1	Niemeyer et al (1985) ¹³⁷	W	German	Me
1	Reff-Eberwein et al (1985) ¹³⁸	W	German	Me
1	Shear (1985) ¹³⁹	W	English	Me
1	Spitzer & Steinhäusern (1985) ¹⁴⁰	W	German	Me
1	Takita et al (1985) ¹⁴¹	E	Japanese	Me
3	Weerheijm & van der Waal (1985) ¹⁴²	W	Dutch	Me
1	Zachariades et al (1985) ¹⁴³	W	English	Me
1	Arafat & Lunin (1984) ¹⁴⁴	W	English	Me
1	Saviano (1984) ¹⁴⁵	W	Italian	Me
1	Chuong et al (1982) ¹⁴⁶	W	English	Me
1	Sakamoto et al (1982) ¹⁴⁷	E	English	Me
1	Li (1981) ¹⁴⁸	E	Chinese	Me
1	Voorsmit et al (1981) ¹⁴⁹	W	English	Me
1	Buffetaud et al (1980) ¹⁵⁰	W	French	Me
1	Jain & Kherdekar (1980) ¹⁵¹	W	English	Me
1	Lechien et al (1980) ¹⁵²	W	French	Me
1	Martinez et al (1980) ¹⁵⁴	W	French	Me

Appendix Continued

<i>Selection criterion</i>	<i>Report (First author's surname and date of publication)</i>	<i>Global group</i>	<i>Language of publication</i>	<i>Database</i>
1	Vedtofte & Praetorius (1979) ¹⁵⁵	W	English	Me
1	Hodgkinson et al (1978) ¹⁵⁶	W	English	Me
1	Rachanis and Shear (1978) ⁶⁸	W	English	Me
1	Smith & Shear (1978) ¹⁵⁷	W	English	Me
1	Isberg-Holm (1977) ¹⁵⁸	W	English	Me
1	Rengaswamy (1977) ¹⁵⁹	E	English	Me
1	Browne (1976) ¹⁶⁰	W	English	Me
1	Eversole et al (1975) ¹⁶¹	W	English	Me
A	Mosadomi et al (1975) ¹⁶²	A	English	Me
1	Forssell et al (1974) ¹⁶³	W	English	Me
1	Klammt (1973) ¹⁶⁴	W	German	Me
1	Radden & Reade (1973) ¹⁶⁵	W	English	Me
1	Calonius et al (1972) ¹⁶⁶	W	English	Me
1	Donoff et al (1972) ¹⁶⁷	W	English	Me
1	McIvor (1972) ¹⁶⁸	W	English	Me
1	Payne (1972) ¹⁶⁹	W	English	Me
1	Fickling (1965) ¹⁷⁰	W	English	Me

Global group A, sub-Saharan African; L, Latin American; E, East Asian; W, Western; Me, MEDLINE Database; Li, LILACS; R, reference harvesting; H, hand-searching.

Criterion 1. Giardina et al report⁹⁵ was excluded because they did not disclose the type of keratinization. Nevertheless, if they had been included they would have been excluded later under criterion 3.

Criterion 3. It is clear that de Paula et al 10 uninfamed parakeratotic cases must have been selected.¹⁰⁰

Criterion A. Although Avelar et al 2008 report⁷⁰ was more recent, not only did it substantially report the detail reported by Antunes et al earlier report,⁵³ but the latter was more detailed and therefore retained as a SR-included report, the former was excluded.