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Surgical Management of Odontogenic Keratocyst and Recurrence: A Multicenter Retrospective Study

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Abstract

Background: Odontogenic keratocysts (OKC) recur frequently. We evaluated surgical outcomes and predictors of recurrence in OKC, using orthokeratinized odontogenic cysts (OOC) as a comparison group. **Methods**: In this multicenter retrospective study, 113 consecutive patients (54 OKC, 59 OOC) treated in four northwestern Italian centres in 2015–2025 were included. Recurrence-free survival was analysed with Kaplan–Meier and Cox methods (107 patients with ≥12 months' follow-up); initial treatment was compared within OKC, and a sensitivity analysis excluded patients operated on before 2015. **Results**: Median follow-up was 4 years. A first recurrence occurred in 40/54 OKC (74.1%; 95% CI 60.3–85.0%) and 7/59 OOC (11.9%); 5-year recurrence-free survival was 37.0% versus 70.9% ($p < 0.001$), and OKC histotype was the only independent predictor (hazard ratio 5.76; 95% CI 2.47–13.45). Within OKC, initial treatment was not associated with recurrence ($p = 0.810$); in the incident cohort, the recurrence rate was 72.5%. None of the eight patients treated with adjuvant therapy (three OKC with topical 5-fluorouracil) recurred after a median follow-up of 2.5 years. **Conclusions**: In this real-world series, three-quarters of OKC recurred, and histotype was the dominant prognostic factor; the absence of recurrence after adjuvant therapy is hypothesis-generating and requires prospective confirmation with long-term follow-up.

Keywords: odontogenic keratocyst; orthokeratinized odontogenic cyst; recurrence; histotype; surgical treatment; 5-fluorouracil; cryotherapy; Kaplan–Meier; jaw cyst

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1. Introduction

The odontogenic keratocyst (OKC) is a developmental intraosseous cyst of odontogenic origin, arising from remnants of the dental lamina or, less frequently, from basal cells of the overlying oral epithelium [1,2]. First described by Philipsen in 1956 as a distinct entity defined by its characteristic keratinised epithelial lining, OKC has attracted considerable scientific interest owing to its aggressive biological behaviour, high recurrence rate, and

potential association with hereditary syndromes [1,3]. OKC accounts for approximately 10–15% of all odontogenic cysts, representing the third most common jaw cyst after radicular and dentigerous cysts across most populations [4,5]. Large epidemiological series have confirmed this figure across diverse geographic settings; a recent retrospective analysis of 19,352 histologically confirmed jaw cysts spanning nearly five decades found radicular cysts to be the most prevalent, followed by dentigerous cysts and OKC, with some regional variation [6].

OKC demonstrates a broad age distribution, with a peak incidence in the second and third decades of life and a secondary peak in older age groups [3,7]. A slight male predominance is consistently reported, with male-to-female ratios typically ranging from 1.3:1 to 1.5:1 in large series [8,9]. The posterior mandible, particularly the angle, ramus and molar–premolar region, is the most frequently involved site, accounting for approximately 60–70% of cases [9,10]. Maxillary involvement is observed in approximately 20–35% of cases and tends to affect the posterior region or premaxilla. Clinically, OKC is often asymptomatic until the lesion reaches a considerable size, as it grows preferentially along the medullary cavity with minimal cortical expansion [3,7]. Radiographically, OKC presents as a well-defined unilocular or multilocular radiolucency with smooth corticated margins, which may be associated with an impacted tooth and may mimic an ameloblastoma or a dentigerous cyst [3,11].

Histologically, OKC is characterised by a thin, uniform parakeratinized stratified squamous epithelium, typically five to eight cell layers thick, with a corrugated parakeratin surface layer and a well-defined basal cell layer of columnar or cuboidal cells with hyperchromatic nuclei oriented perpendicularly to the basement membrane [7]. The cyst wall is usually thin and fibrous, with a characteristic paucity of inflammatory infiltrate. A clinically critical feature is the frequent presence of satellite (daughter) cysts, epithelial islands, and budding projections within the fibrous wall, which are widely recognised as major contributors to incomplete surgical removal and subsequent recurrence [11]. The orthokeratinized odontogenic cyst (OOC), originally described by Wright as an orthokeratinized variant of OKC [12], is classified by the 2017 and 2022 editions of the World Health Organization (WHO) Classification of Head and Neck Tumours as a distinct clinicopathological entity: it exhibits a uniform orthokeratinized epithelial lining with a subjacent granular cell layer and a flattened, non-palisaded basal layer, lacks PTCH1 mutations, is not associated with Gorlin–Goltz syndrome, and recurs in fewer than 5% of cases after enucleation [13–18].

Mutations of the tumour suppressor gene PTCH1, which encodes a transmembrane receptor that inhibits Smoothened in the Sonic Hedgehog (SHH) signalling pathway, represent the most consistently identified molecular alteration of OKC: they are found in more than 80% of syndromic and in 35–80% of sporadic cases and result in constitutive SHH activation with aberrant epithelial proliferation and impaired apoptosis [19]. Immunohistochemical studies have demonstrated higher Ki-67 labelling indices in OKC than in non-keratinised odontogenic cysts, and a high Ki-67 expression in the basal layer has been proposed as a potential prognostic marker of recurrence after enucleation [20].

The nosological position of OKC has changed repeatedly. Classified as a developmental cyst in the 1971 and 1992 WHO editions, it was designated ‘keratocystic odontogenic tumour’ in 2005 on the basis of its aggressive behaviour, high proliferative activity and PTCH1 mutations, and was returned to the cyst category in the 2017 and 2022 editions, which also recognised OOC as an independent entity [13–17]. Beyond taxonomy, this debate has practical implications: a neoplastic designation has been associated with more aggressive surgical management, whereas a cystic classification supports conservative approaches in selected cases.

A clinically important association is that between OKC and Gorlin–Goltz syndrome (GGS), also known as nevoid basal cell carcinoma syndrome, an autosomal dominant condition caused by germline mutations in PTCH1 [21]. OKCs are found in 75–80% of patients with GGS, frequently as multiple synchronous or metachronous lesions in the first and second decades of life, and syndromic OKCs recur more often than sporadic lesions because of a greater number of satellite cysts, epithelial islands and basal cell budding [21,22]. The recognition of multiple OKCs, particularly in young patients, should therefore prompt systematic evaluation for GGS. Although rare, malignant transformation of OKC into primary intraosseous squamous cell carcinoma has been reported, with an estimated incidence of dysplasia and malignant change of approximately 2.8% in large case series, often associated with chronic inflammation and repeated recurrences [23].

Because of the high recurrence rate and aggressive behaviour of OKC, a wide spectrum of surgical approaches has been described, ranging from conservative enucleation to radical resection. Intermediate options include enucleation with peripheral ostectomy, enucleation combined with chemical adjuvants (Carnoy's solution or modified formulations), enucleation with cryotherapy, enucleation with topical 5-fluorouracil (5-FU), and marsupialisation with or without secondary enucleation [24,25]. A systematic review by Blanas et al. reported recurrence rates of 17–56% following simple enucleation [24]. Subsequent large meta-analyses have attempted to define the optimal surgical strategy: Al-Moraissi et al. reported recurrence rates of 23.1% for enucleation alone, 11.5% for enucleation with Carnoy's solution, 14.5% for enucleation with cryotherapy, and 8.4% for wide resection, with marsupialisation alone showing the highest rate at 32.3% [25]. A short communication by Titinchi (2020), which pooled recurrence data from five systematic reviews, proposed a management protocol in which the surgical approach is determined by lesion size, patient age, proximity to vital structures, accessibility, cortical or soft-tissue perforation and recurrent status, with enucleation plus adjuvant methods for accessible lesions of limited size and decompression followed by enucleation with adjuvants as an acceptable first-line treatment [26]. The role of topical 5-FU has gained increasing attention; a 2022 systematic review and meta-analysis by Singh et al. found no recurrences among 56 patients treated with 5-FU [27], corroborated by a 2024 systematic review and meta-analysis, which demonstrated that 5-FU was associated with a significantly lower recurrence rate and lower rates of permanent nerve injury compared with modified Carnoy's solution (MCS) [28]. Marsupialisation followed by delayed enucleation has been advocated for large lesions, as preliminary decompression promotes cyst shrinkage and facilitates more complete secondary removal [29], although a meta-analysis found fewer recurrences after primary enucleation than after decompression-based strategies [30]. Despite this evidence base, there is no consensus on treatment: different protocols coexist, and management must balance recurrence risk against procedural morbidity, lesion size, histotype, and syndromic status [31].

The aim of the present multicenter retrospective study was to describe the surgical approaches used for OKC in four surgical departments, ranging from conservative to more aggressive techniques, and to assess their outcomes in terms of recurrence, analysed as a time-to-event outcome. In line with the current WHO classification, lesions lined by orthokeratinized epithelium were analysed separately as OOC and used as a comparison group. In addition, the study investigated clinical, demographic and histopathological variables associated with recurrence, with the aim of identifying prognostic factors to guide individualised management and surveillance.

2. Materials and Methods

2.1. Study Design and Patient Population

This multicenter retrospective study was conducted in the Departments of Maxillofacial Surgery and Odontostomatology of four institutions in northwest Italy: Città della Salute e della Scienza Hospital (Turin), Martini Hospital (Turin), Santa Croce e Carle Hospital (Cuneo) and Cardinal Massaja Hospital (Asti). Patients with a histological diagnosis of keratinising odontogenic cyst (OKC or OOC) were consecutively retrieved from the institutional surgical databases of the period 2015–2025, which were queried for the diagnosis 'keratocyst'. Inclusion criteria comprised a histologically confirmed diagnosis and the availability of clinical and radiological records documenting treatment and recurrence status; patients with incomplete clinical or radiological records were excluded. The query retrieved 170 records; 57 patients (33.5%) were excluded because of incomplete clinical or radiological records, and the remaining 113 patients constituted the descriptive cohort (flow diagram in Supplementary Figure S1). No minimum duration of follow-up was required for inclusion, and no patient was excluded because of short follow-up. An exact follow-up duration of at least 12 months in all cases was available for 107 patients; six patients whose follow-up was recorded only as shorter than 12 months, without an exact duration, were retained in the descriptive analyses but excluded from the time-to-event analyses, which were therefore based on a minimum documented follow-up of 12 months. The follow-up of all patients was updated in 2025, when the databases were compiled, and the year of the primary operation was obtained from the clinical records. Because the surgical databases were queried for the activity of 2015–2025, patients whose primary operation preceded 2015 could enter the cohort only if they underwent surgery for a recurrence within that window: this was the case for 3 of the 113 patients (all with OKC), whereas the remaining 110 patients (51 OKC and 59 OOC) had their primary operation in 2015 or later and constitute the incident cohort used in the sensitivity analysis described in Section 2.4; the implications of this retrieval strategy are discussed in the Limitations section. The study is reported in accordance with the STROBE recommendations for observational studies (Supplementary Table S1).

2.2. Histopathological Diagnosis

All lesions were diagnosed by the Pathology Department of the treating institution on haematoxylin–eosin sections of the enucleated specimen or of the incisional biopsy, according to the criteria of the 4th (2017) and 5th (2022) editions of the WHO Classification of Head and Neck Tumours [13–16]. Lesions lined by a thin, corrugated parakeratinized epithelium with a palisaded basal cell layer were classified as OKC; lesions lined by an orthokeratinized epithelium with a prominent granular layer and a flattened basal layer were classified as OOC. Slides were not centrally re-reviewed for the purpose of this study. Because OOC is now considered a distinct entity, the primary analysis, including the comparison of initial treatments, was restricted to OKC, and OOC was analysed as a separate comparison group.

2.3. Data Collection

Demographic and clinical data were collected from the clinical records and included age at the primary operation, sex, comorbidity, lesion site, teeth involved, histotype, pre- and postoperative imaging, primary surgical treatment, duration of follow-up, recurrence and its timing, and the treatment of each recurrence. Comorbidity was recorded as a binary variable, defined as the presence of at least one systemic disease documented in the clinical record at the time of surgery (malignant neoplasm, cardiovascular disease, diabetes mellitus, chronic inflammatory disease, or a genetic syndrome); the single patient with

GGS was included in this category, and syndromic status was also recorded separately. Lesion size, locularity, cortical perforation and the presence of daughter cysts were not systematically recorded in the institutional databases, and lesion size could not be retrieved retrospectively from the stored imaging.

Primary surgical treatment was grouped into four clinically meaningful categories: excision alone, consisting of enucleation of the cyst followed by curettage of the bony cavity, without peripheral ostectomy and without chemical or cryogenic adjuvants (peripheral ostectomy was not performed in any patient of this category in any centre); excision plus adjuvant therapy, consisting of enucleation and curettage followed by the application of cryotherapy or of topical 5-FU to the bony cavity; excision plus reconstruction (local flap, reconstruction plate or bone graft); and conservative procedures (marsupialization or decompression with a drainage tube without documented secondary enucleation). Topical 5-FU was applied as 5% 5-fluorouracil cream (Flonida 5%; A. Menarini India Pvt. Ltd., Mumbai, India) spread on a gauze that was packed into the bony cavity immediately after enucleation and curettage and removed after 5 days, a protocol that differs from the 24 h application described by Caminiti et al. [32] only in the longer dwell time. Cryotherapy consisted of the intraoperative application to the bony cavity, after enucleation and curettage, of a hydrofluorocarbon-based cryogenic spray (Crio Spray; Karl, Sanremo, Italy); the number and duration of the applications were not recorded, and liquid nitrogen was not used. For the time-to-event analyses, in which the last three categories were too sparse to be analysed separately, treatment was also dichotomised as excision alone versus other initial treatments.

The primary outcome was recurrence, defined as the reappearance of a radiolucent lesion at the site of a previously treated cyst during follow-up, documented by panoramic radiography, computed tomography (CT) or cone-beam CT, and confirmed histologically after re-intervention. Three recurrence stages were defined: stage I, the first recurrence after primary treatment; stage II, a further recurrence after surgical treatment of the first recurrence; stage III, a further recurrence after treatment of the second recurrence. The variable ‘surgical treatment’ refers to the primary treatment; the treatments of stage I and stage II recurrences (salvage treatments) are reported separately. Follow-up duration was calculated from the date of the primary surgical treatment to the date of the last documented clinical or radiological assessment. In the institutional databases, follow-up duration and time to recurrence were recorded in whole years, and the exact dates (month) of the primary operation, of the diagnosis of recurrence, and of the last visit could not be retrieved from the clinical records; all time-to-event analyses were therefore conducted at a yearly resolution, and the statement that no recurrence was recorded before 12 months refers to the recorded times (see Limitations). For the time-to-event analyses, the outcome was time to first recurrence, defined as the interval between the primary surgical treatment and the diagnosis of the first recurrence; patients who did not experience recurrence were right-censored at the date of their last documented follow-up. For stages II and III, time to recurrence was measured from the treatment of a recurrence to the diagnosis of the subsequent one.

All centres adopted the same postoperative surveillance schedule, with clinical examination at 1 and 2 weeks and at 1, 3, 6 and 12 months after surgery and yearly thereafter, and panoramic radiography at the follow-up visits, supplemented by CT or cone-beam CT when a recurrence was suspected or when the lesion involved the maxillary sinus or the inferior alveolar canal. Among the 105 patients with a recorded modality, postoperative imaging consisted of panoramic radiography alone in 70 (66.7%), panoramic radiography plus CT in 22 (21.0%), panoramic radiography plus cone-beam CT in 10 (9.5%), and CT or cone-beam CT alone in 3 (2.9%). Cross-sectional imaging was used during follow-up in

18/61 patients (29.5%) treated in Cuneo and in 17/44 (38.6%) treated in the three Turin-area centres. The distribution of patients, histotypes, follow-up and first recurrences by centre is reported in Section 3.7.

2.4. Statistical Analysis

Continuous variables are reported as mean ± standard deviation (SD) or as median with interquartile range (IQR) and range, as appropriate; categorical variables are reported as frequencies and percentages, with exact binomial (Clopper–Pearson) 95% confidence intervals (CI) for the reported recurrence proportions. OKC and OOC were compared with the two-sample *t*-test (age) and Fisher's exact test (categorical variables); Fisher's exact test was preferred to the chi-square test because several categories were sparse. Within the OKC group, patients with and without a first recurrence were compared in the same way. No formal sample size calculation was performed, because all consecutive eligible patients of the study period were included; with 47 first-recurrence events, the multivariable model was limited to four covariates in order to respect the usual requirement of approximately ten events per variable.

Time-to-first-recurrence analyses were conducted in the 107 patients with an exact follow-up duration of at least 12 months. Because the earliest recorded time to recurrence was 1 year, the six patients with a shorter follow-up did not contribute to any risk set at the yearly resolution of the recorded data, and their exclusion did not change the Kaplan–Meier estimates, the log-rank tests or the Cox model (verified by repeating the analyses with these six patients included and censored at 6 months); five of the six belonged to the group of other initial treatments, which therefore decreased from 21 to 16 patients (a quarter of that group), and one to the excision-alone group (92 to 91). Univariable time-to-event analyses were performed using Kaplan–Meier estimates and log-rank tests. Multivariable analysis was performed using Cox proportional hazards regression. Age was included as a continuous variable, whereas histotype, lesion site and comorbidity were included as categorical variables; these variables were selected on the basis of clinical relevance and prior evidence. Because the treatment group did not satisfy the proportional hazards assumption, and because no recurrence occurred in the adjuvant therapy group, which makes a hazard ratio for the four treatment categories non-estimable, the final Cox model was stratified by initial treatment group. The treatment categories were unevenly distributed between histotypes (all five patients treated with cryotherapy and six of the ten patients treated conservatively had an OOC), so that a comparison of initial treatments in the pooled cohort would be confounded by histotype, the dominant prognostic factor; in accordance with the primary analysis, the comparison of initial treatment (excision alone versus other initial treatments) was therefore performed within the OKC group, with Kaplan–Meier estimates and the log-rank test, and a separate multivariable Cox model restricted to OKC was fitted with age, lesion site and comorbidity as covariates (40 events in 52 patients, i.e., about 13 events per covariate) and stratified by initial treatment group. As a sensitivity analysis addressing the retrieval of patients from the surgical activity of 2015–2025, the recurrence rate of OKC, with its exact 95% CI, and the Kaplan–Meier recurrence-free survival at 5 years were re-estimated in the subset of OKC whose primary operation was performed in 2015 or later (incident cohort) and compared with the subset operated on before 2015. Hazard ratios (HR) with 95% CI are reported. The proportional hazards assumption was assessed using tests based on scaled Schoenfeld residuals, with event times transformed using the Kaplan–Meier survival function. Tied event times, which were frequent because of the yearly resolution of the recorded times, were handled using the Efron method. The second and third recurrences were summarised descriptively because of the limited number of events (9 and 3, respectively). All tests were two-sided,

and a p-value < 0.05 was considered statistically significant; given the exploratory nature of the subgroup comparisons, no adjustment for multiplicity was applied and p-values should be interpreted accordingly. Analyses were performed using Minitab Statistical Software, version 21.2 (Minitab, LLC, State College, PA, USA) and Python, version 3.12 (Python Software Foundation, Wilmington, DE, USA), with the SciPy (version 1.17) and lifelines (version 0.30) libraries.

3. Results

3.1. Study Population

The study cohort comprised 113 patients (78 men and 35 women; male-to-female ratio 2.2:1) with a mean age of 47.0 ± 19.2 years (median 45; range 11–98). Fifty-four lesions (47.8%) were OKC, and 59 (52.2%) were OOC. The clinical and demographic characteristics of the two groups are summarised in Table 1. Patients with OKC tended to be older (50.2 ± 19.4 vs. 44.1 ± 18.7 years; p = 0.094) and had comorbidities more frequently (27.8% vs. 10.2%; p = 0.028), whereas sex distribution and lesion site did not differ. Comorbidities consisted of a malignant neoplasm in eight patients (prostate carcinoma in three, breast carcinoma in two, colon carcinoma, leukaemia and multiple myeloma in one each), cardiovascular disease in seven (arterial hypertension in five, previous myocardial infarction and stroke in one each), diabetes mellitus in six (two of whom also had hypertension), Crohn's disease in one and GGS in one (0.9%); the only syndromic patient was an 18-year-old woman with a mandibular OKC. The mandible was involved in 79 patients (69.9%): quadrant IV in 29, quadrant III in 24, body and ramus in 23 and ramus alone in 3; maxillary lesions (n = 34) involved quadrant I in 14, quadrant II in 10 and the premaxilla in 10. The distribution of patients by centre is reported in Section 3.7.

Table 1. Clinical and demographic characteristics, treatment, follow-up and recurrence of the 113 patients by histotype. Age is expressed as mean ± standard deviation (SD) and median (range); categorical variables as n (%). p-values refer to the comparison between odontogenic keratocyst (OKC) and orthokeratinised odontogenic cyst (OOC): two-sample t-test for age, Mann–Whitney test for follow-up and Fisher's exact test for categorical variables. Follow-up refers to the 107 patients with an exact follow-up duration of at least 12 months. CI, confidence interval; IQR, interquartile range; 5-FU, 5-fluorouracil.

Variable	OKC (n = 54)	OOC (n = 59)	Total (n = 113)	p-Value
Age, years, mean ± SD	50.2 ± 19.4	44.1 ± 18.7	47.0 ± 19.2	0.094
Age, years, median (range)	51.5 (11–98)	40 (12–84)	45 (11–98)	
Sex, male	36 (66.7)	42 (71.2)	78 (69.0)	0.685
Comorbidity	15 (27.8)	6 (10.2)	21 (18.6)	0.028
Site				
Maxilla	14 (25.9)	20 (33.9)	34 (30.1)	0.414
Mandible	40 (74.1)	39 (66.1)	79 (69.9)	
Primary surgical treatment				
Excision alone	44 (81.5)	48 (81.4)	92 (81.4)	1.000
Excision + adjuvant therapy	3 (5.6)	5 (8.5)	8 (7.1)	
Excision + topical 5-FU	3	0	3	
Excision + cryotherapy	0	5	5	
Excision + reconstruction	3 (5.6)	0	3 (2.7)	
Excision + flap reconstruction	2	0	2	
Excision + reconstruction plate	1	0	1	
Conservative procedures	4 (7.4)	6 (10.2)	10 (8.8)	
Decompression (drainage tube)	3	6	9	
Marsupialization	1	0	1	

Table 1. *Cont.*

Variable	OKC (*n* = 54)	OOC (*n* = 59)	Total (*n* = 113)	*p*-Value
Follow-up, years, median (IQR; range); *n* with exact duration	6 (3–8; 1–23); *n* = 52	2 (1–4; 1–6); *n* = 55	4 (2–6; 1–23); *n* = 107	<0.001
First recurrence, *n* (%; 95% CI)	40 (74.1; 60.3–85.0)	7 (11.9; 4.9–22.9)	47 (41.6; 32.4–51.2)	<0.001
Time to first recurrence, years, median (range)	2 (1–15)	2 (1–5)	2 (1–15)	
Second recurrence, *n*/*n* with first recurrence	8/40	1/7	9/47	
Third recurrence, *n*/*n* with second recurrence	3/8	0/1	3/9	

Primary treatment consisted of excision alone in 92 patients (81.4%), excision plus adjuvant therapy in 8 (7.1%; topical 5-FU in 3 and cryotherapy in 5), excision plus reconstruction in 3 (2.7%) and conservative procedures in 10 (8.8%; decompression with a drainage tube in 9 and marsupialisation in 1); the distribution of treatments did not differ between OKC and OOC (Table 1). An exact follow-up duration of at least 12 months was available for 107 patients, who were included in the time-to-event analyses; the six patients whose follow-up was recorded only as shorter than 12 months (2 OKC and 4 OOC) were all free of recurrence; five of them had received other initial treatments (decompression with a drainage tube in 4 and excision plus flap reconstruction in 1) and one excision alone. The primary operation had been performed in 2015 or later in 110 patients (51 OKC and 59 OOC) and before 2015 in 3 (all with OKC), the latter having entered the cohort because of a re-intervention for recurrence during the study period. In this analytical cohort the median follow-up was 4 years (IQR 2–6; range 1–23): 6 years (IQR 3–8; range 1–23) in OKC and 2 years (IQR 1–4; range 1–6) in OOC ($p < 0.001$), and 4 years (IQR 2–6; range 1–23) in the excision group versus 2 years (IQR 1–5; range 1–10) in the other-treatment group; 45 patients (42.1%) had at least 5 years and 8 (7.5%) at least 10 years of follow-up.

3.2. First Recurrence and Time-to-Event Analysis

A first recurrence was recorded in 47 patients (41.6%; 95% CI 32.4–51.2%), all of whom underwent re-intervention with histological confirmation. The recurrence rate was 74.1% (40/54; 95% CI 60.3–85.0%) in OKC and 11.9% (7/59; 95% CI 4.9–22.9%) in OOC (odds ratio 21.2; 95% CI 7.8–57.5; $p < 0.001$). In the crude comparison, patients with recurrence were older than those without (51.5 ± 20.0 vs. 43.8 ± 18.1 years; $p = 0.037$), whereas sex (30/78 men, 38.5%, vs. 17/35 women, 48.6%; $p = 0.409$), comorbidity (12/21, 57.1%, vs. 35/92, 38.0%; $p = 0.142$), and site (11/34 maxillary, 32.4%, vs. 36/79 mandibular lesions, 45.6%; $p = 0.217$) were not associated with recurrence. The median time to first recurrence was 2 years (IQR 2–5; range 1–15); 9 of the 47 recurrences (19.1%), all in OKC, were diagnosed more than 5 years after primary surgery.

Kaplan–Meier analysis showed a significantly lower recurrence-free survival for OKC than for OOC (log-rank $\chi^2 = 15.28$; $p < 0.001$; Figure 1): the estimated recurrence-free survival at 1, 2 and 5 years was 84.6% (95% CI 72–92%), 59.0% (44–71%) and 37.0% (24–51%) for OKC, compared with 98.2% (88–100%), 90.4% (76–96%) and 70.9% (43–87%) for OOC; at 10 years the estimate for OKC was 13.3% (95% CI 4–28%). The median recurrence-free survival was 3 years in OKC and was not reached in OOC. Initial treatment was not compared in the pooled cohort because the treatment categories were unevenly distributed between histotypes (all five patients treated with cryotherapy and six of the ten patients treated conservatively had an OOC), and such a comparison would be confounded by

histotype; the comparison within OKC is reported in Section 3.3 and Figure 2. In the initial Cox model, the treatment group did not satisfy the proportional hazards assumption ($p = 0.014$) and was therefore used as a stratification variable in the final model, whose results are summarised in Table 2A. OKC histotype was the only independent predictor of first recurrence (HR 5.76; 95% CI 2.47–13.45; $p < 0.001$), whereas age (HR 0.98 per year; 95% CI 0.97–1.00; $p = 0.109$), lesion site (maxilla vs. mandible: HR 0.71; 95% CI 0.35–1.42; $p = 0.331$) and comorbidity (yes vs. no: HR 0.74; 95% CI 0.32–1.70; $p = 0.475$) were not independently associated with first recurrence. The proportional hazards assumption was satisfied for all covariates in the final model (all $p > 0.2$). The association between older age and recurrence observed in the crude comparison therefore disappeared once follow-up time and histotype were accounted for, a discrepancy that most likely reflects the longer follow-up and the older age of patients with OKC.

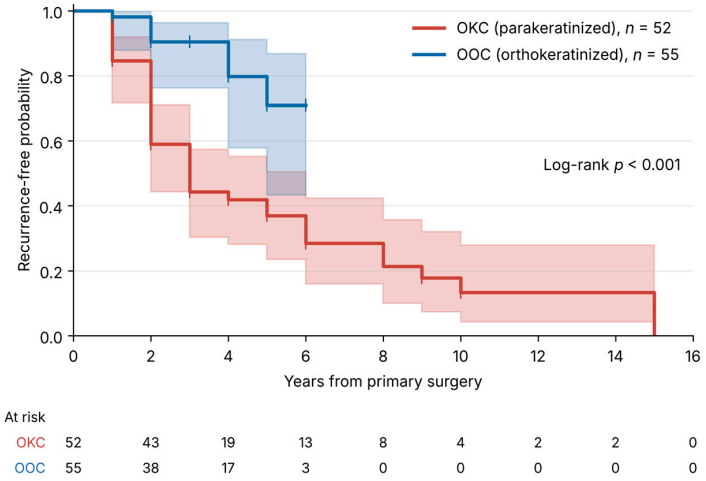


Figure 1. Kaplan–Meier estimates of recurrence-free survival after primary surgery according to histotype in the 107 patients with at least 12 months of documented follow-up (parakeratinised odontogenic keratocyst, OKC, $n = 52$; orthokeratinised odontogenic cyst, OOC, $n = 55$). Shaded areas represent 95% confidence intervals, tick marks indicate censored patients and the number of patients at risk is shown below the graph; because follow-up and time to recurrence were recorded in whole years, the curves step at yearly intervals. Recurrence-free survival was significantly lower for OKC (log-rank $p < 0.001$).

Table 2. Multivariable Cox proportional hazards regression for time to first recurrence. (A) Whole time-to-event cohort: the model included the 107 patients with at least 12 months of documented follow-up and the 47 first-recurrence events and was stratified by initial treatment group (excision alone versus other initial treatments); treatment group was therefore not assigned a separate hazard ratio. (B) OKC only: the model included the 52 OKC with at least 12 months of documented follow-up and the 40 first-recurrence events and was stratified by initial treatment group. Tied event times were handled using the Efron method. CI, confidence interval; HR, hazard ratio; OKC, odontogenic keratocyst (parakeratinised); OOC, orthokeratinised odontogenic cyst.

Predictor	Comparison or Unit	HR	95% CI	*p*-Value
(A) Whole time-to-event cohort ($n = 107$; 47 first recurrences), stratified by initial treatment group				
Age	Per 1-year increase	0.98	0.97–1.00	0.109
Histotype	OKC vs. OOC	5.76	2.47–13.45	<0.001
Comorbidity	Yes vs. no	0.74	0.32–1.70	0.475
Site	Maxilla vs. mandible	0.71	0.35–1.42	0.331
(B) OKC only ($n = 52$; 40 first recurrences)				
Age	Per 1-year increase	0.98	0.96–1.00	0.033
Comorbidity	Yes vs. no	0.92	0.41–2.11	0.853
Site	Maxilla vs. mandible	0.80	0.38–1.68	0.552

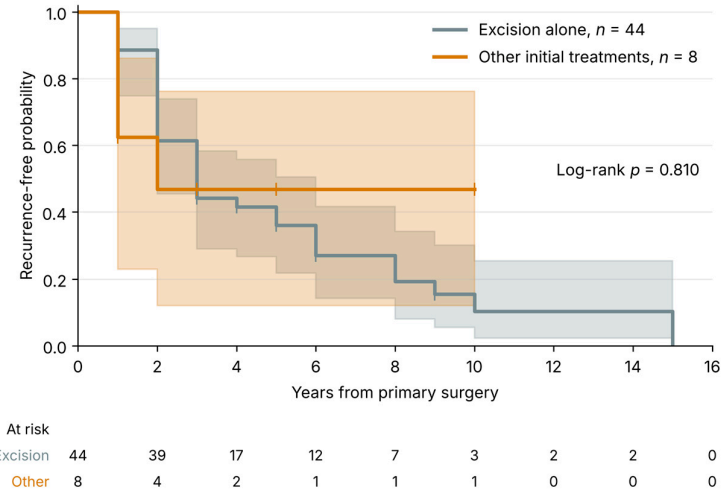


Figure 2. Kaplan–Meier estimates of recurrence-free survival according to initial treatment group within the 52 odontogenic keratocysts (OKC) with at least 12 months of documented follow-up: excision alone (n = 44) versus other initial treatments (excision plus topical 5-fluorouracil, excision plus reconstruction or conservative procedures; n = 8). Shaded areas represent 95% confidence intervals, tick marks indicate censored patients and the number of patients at risk is shown below the graph; because follow-up and time to recurrence were recorded in whole years, the curves step at yearly intervals. Recurrence-free survival did not differ significantly between the two groups (log-rank p = 0.810).

3.3. Initial Treatment and Predictors of Recurrence Within OKC

In the binary comparison within the 54 OKC, recurrence was not associated with age (51.9 ± 20.1 vs. 45.4 ± 17.3 years; p = 0.285), sex (69% in men vs. 83% in women; p = 0.339), comorbidity (80% vs. 72%; p = 0.733) or site (71% in the maxilla vs. 75% in the mandible; p = 1.000). The only patient with GGS, treated by excision alone, recurred 2 years after surgery and was free of further recurrence after re-excision. Recurrence occurred in 36/44 OKC treated with excision alone (81.8%), in 0/3 treated with excision plus 5-FU, in 1/3 treated with excision plus reconstruction and in 3/4 treated conservatively; the difference between the adjuvant group and the other OKC (0/3 vs. 40/51, 78.4%; p = 0.015) must be read in the light of the three-patient denominator.

In the 52 OKC of the time-to-event cohort (40 first recurrences), recurrence-free survival did not differ significantly between the 44 patients treated with excision alone and the 8 patients who received other initial treatments (log-rank χ^2 = 0.06; p = 0.810; Figure 2): the estimated recurrence-free survival at 1, 2 and 5 years was 88.6%, 61.4% and 36.0% after excision alone (36 events) and 62.5%, 46.9% and 46.9% after other initial treatments (4 events). In the Cox model restricted to OKC (Table 2B), older age was associated with a lower hazard of first recurrence (HR 0.98 per year; 95% CI 0.96–1.00; p = 0.033), whereas lesion site (maxilla vs. mandible: HR 0.80; 95% CI 0.38–1.68; p = 0.552) and comorbidity (yes vs. no: HR 0.92; 95% CI 0.41–2.11; p = 0.853) were not independently associated with first recurrence; the proportional hazards assumption was satisfied for all covariates (all p > 0.33). The treatment group violated the proportional hazards assumption within OKC as well (p = 0.011) and was therefore used as a stratification variable; in an unstratified model including the treatment dichotomy as a covariate, the estimates were similar and other initial treatments were not associated with recurrence (HR 1.02 vs. excision alone; 95% CI 0.35–3.03; p = 0.966).

The primary operation had been performed in 2015 or later in 51 of the 54 OKC and before 2015 in 3, all of whom had recurred and had entered the cohort because of the re-intervention for recurrence. In the incident OKC cohort (median follow-up 5 years; IQR 2–8;

range 1–10), the recurrence rate was 37/51 (72.5%; 95% CI 58.3–84.1%), whereas all three OKC operated on before 2015 had recurred, and the estimated recurrence-free survival at 1, 2 and 5 years was 83.7%, 58.6% and 34.9% (95% CI at 5 years 21–49%), compared with 84.6%, 59.0% and 37.0% in the full OKC cohort.

3.4. Orthokeratinized Odontogenic Cysts

Among the 59 OOC, seven recurrences were recorded: three after decompression with a drainage tube without secondary enucleation and four after excision alone, 1–5 years after the primary operation; one of these patients recurred a second time. None of the five OOC treated with excision plus cryotherapy recurred during a follow-up of 1–5 years.

3.5. Patients Treated with Adjuvant Therapy

The eight patients treated with excision plus adjuvant therapy are listed in Table 3. They comprised three OKCs treated with topical 5-FU (age 44–70 years; two mandibular and one maxillary lesion; follow-up 1, 3 and 5 years) and five OOCs treated with cryotherapy (age 22–54 years; three mandibular and two maxillary lesions; follow-up 1–5 years). The median follow-up of the eight patients was 2.5 years (range 1–5; 3 years, range 1–5, in the three OKC treated with 5-FU), that is, barely longer than the median time to first recurrence of 2 years observed in the whole cohort, so that a substantial proportion of the recurrences expected in this group could not yet have been observed. No recurrence was observed in this group (0/8; 0%; 95% CI 0–36.9%), compared with 47 recurrences among the remaining 105 patients (44.8%; 95% CI 35.0–54.8%; Fisher's exact test $p = 0.020$). Given the small size of the adjuvant-treatment subgroup and the absence of events, this finding was considered descriptive and should be interpreted cautiously. Lesion size was not available for these patients.

Table 3. Patients treated with excision plus adjuvant therapy ($n = 8$). F, female; M, male; OKC, odontogenic keratocyst; OOC, orthokeratinised odontogenic cyst; 5-FU, topical 5-fluorouracil.

Patient	Histotype	Adjuvant	Sex	Age (Years)	Site	Follow-Up (Years)	Recurrence
1	OKC	5-FU	F	70	Mandible, quadrant IV	5	No
2	OKC	5-FU	M	55	Mandible, quadrant III	3	No
3	OKC	5-FU	M	44	Maxilla, quadrant I	1	No
4	OOC	Cryotherapy	M	22	Mandible, right body and ramus	5	No
5	OOC	Cryotherapy	M	33	Mandible, quadrant III	2	No
6	OOC	Cryotherapy	M	54	Premaxilla	1	No
7	OOC	Cryotherapy	M	35	Mandible, quadrant III	1	No
8	OOC	Cryotherapy	M	45	Maxilla, quadrant I	3	No

3.6. Second and Third Recurrences

The treatments of the 47 first recurrences and the subsequent recurrences are summarised in Table 4. First recurrences were treated with excision alone in 30 patients, excision plus cryotherapy in 9, excision plus 5-FU in 3, excision plus bone graft in 2, excision plus reconstruction plate in 2, and excision with alloplastic joint reconstruction in 1. A second recurrence (stage II) occurred in 9/47 patients (19.1%; 95% CI 9.1–33.3%; 8 OKC and 1 OOC) after a median of 2 years (range 1–8) from the treatment of the first recurrence: in 7/30 after excision alone, 1/9 after excision plus cryotherapy, 0/3 after excision plus 5-FU and 1/2 after excision plus reconstruction plate. A third recurrence (stage III) occurred in 3/9 patients (33.3%; 95% CI 7.5–70.1%), all with OKC, at 7, 8 and 12 years from the treatment of the second recurrence. Given the limited number of second- and third-recurrence

events, no formal univariable or multivariable inferential analyses were performed for these outcomes.

Table 4. Salvage treatment of the 47 first recurrences (stage I) and subsequent recurrences (stages II and III). The treatment columns refer to the procedure performed for the recurrence, not to the primary treatment. Second and third recurrences are reported as descriptive frequencies only. OKC, odontogenic keratocyst; OOC, orthokeratinised odontogenic cyst; 5-FU, topical 5-fluorouracil; TMJ, temporomandibular joint.

Treatment of the First Recurrence	*n*	Second Recurrence, *n* (%)	Treatment of the Second Recurrence	*n*	Third Recurrence, *n*
Excision alone	30	7 (23.3)	Excision alone	5	2
Excision + cryotherapy	9	1 (11.1)	Excision + cryotherapy	1	0
Excision + 5-FU	3	0 (0)	Excision + 5-FU	1	0
Excision + bone graft	2	0 (0)	Excision + reconstruction plate	1	1
Excision + reconstruction plate	2	1 (50.0)	Excision + TMJ prosthesis	1	0
Excision + TMJ prosthesis	1	0 (0)			
Total	47	9 (19.1)	Total	9	3
OKC	40	8 (20.0)	OKC	8	3
OOC	7	1 (14.3)	OOC	1	0

3.7. Patients, Follow-Up and Recurrences by Centre

The distribution of patients, histotypes, follow-up and first recurrences by centre is shown in Table 5. Città della Salute e della Scienza Hospital contributed 20 patients (14 OKC and 6 OOC), Martini Hospital 10 (3 OKC and 7 OOC), Cardinal Massaja Hospital 22 (18 OKC and 4 OOC) and Santa Croce e Carle Hospital 61 (19 OKC and 42 OOC); the proportion of OOC therefore ranged from 18% to 70% across centres (Fisher's exact test $p < 0.001$), and median follow-up from 2 to 6 years (Kruskal–Wallis test $p = 0.016$). Among OKC, the first-recurrence rate ranged from 57.1% (8/14) at Città della Salute e della Scienza to 89.5% (17/19) at Santa Croce e Carle Hospital ($p = 0.166$); among OOC, all seven recurrences occurred in the three Turin-area centres (1/6 at Città della Salute e della Scienza, 4/7 at Martini Hospital, 2/4 at Cardinal Massaja Hospital; three of them after decompression without secondary enucleation), whereas none of the 42 OOC treated in Cuneo recurred ($p < 0.001$).

Table 5. Patients, histotype, follow-up and first recurrences by participating centre. Follow-up refers to the patients with an exact follow-up duration of at least 12 months (*n*) and is expressed as median (interquartile range; range). OKC, odontogenic keratocyst; OOC, orthokeratinised odontogenic cyst.

Centre	Patients, *n*	OKC/OOC, *n*	Follow-Up, Years	First Recurrences, *n* (%)	First Recurrences in OKC, *n*/*N* (%)	First Recurrences in OOC, *n*/*N* (%)
Città della Salute e della Scienza, Turin	20	14/6	6 (3–6; 1–11); *n* = 17	9 (45.0)	8/14 (57.1)	1/6 (16.7)
Martini Hospital, Turin	10	3/7	2 (2–5; 1–10); *n* = 7	6 (60.0)	2/3 (66.7)	4/7 (57.1)
Cardinal Massaja Hospital, Asti	22	18/4	5 (2.8–8; 1–23); *n* = 22	15 (68.2)	13/18 (72.2)	2/4 (50.0)
Santa Croce e Carle Hospital, Cuneo	61	19/42	3 (1–5; 1–10); *n* = 61	17 (27.9)	17/19 (89.5)	0/42 (0.0)
Total	113	54/59	4 (2–6; 1–23); *n* = 107	47 (41.6)	40/54 (74.1)	7/59 (11.9)

4. Discussion

4.1. General Considerations and Comparison with the Literature

The present multicenter retrospective study analysed 113 patients with a histologically confirmed keratinising odontogenic cyst treated in four centres of northwest Italy, distinguishing, in accordance with the 2017 and 2022 WHO classifications, 54 parakeratinised OKC from 59 OOC [13–16]. Three findings deserve discussion: the very high recurrence rate of OKC, the large proportion of OOC in a cohort retrieved as 'keratocysts', and the absence of recurrence in the small group of patients treated with adjuvant therapy.

Once the analysis was restricted to true OKC, the recurrence rate was 74.1% (40/54), with an estimated 5-year recurrence-free survival of 37%. This figure is considerably higher than the 17–56% reported by Blanas et al. after simple enucleation [24], the approximately 23% pooled estimate of Al-Moraissi et al. for enucleation alone [25], and the 16% overall recurrence reported in a recent 24-year single-centre series of 291 cases [31]; the pooled figure of 41.6% for the whole cohort appears consistent with the literature only because the OOC dilutes the denominator. Several factors may explain this discrepancy. First, 44 of the 54 OKC (81%) were treated with excision alone, without peripheral ostectomy or chemical adjuvants, which, together with marsupialisation alone, is the approach with the highest recurrence rates in the meta-analyses [24–26]. Second, the four participating centres are referral institutions, and large or multilocular lesions, which carry the highest risk of recurrence [33,34], are likely to be over-represented; lesion size could not be retrieved for this analysis. Third, because patients were retrieved from the surgical databases of the period 2015–2025, patients whose primary operation preceded 2015 could enter the cohort only if they were re-treated for a recurrence within that window, whereas patients treated before 2015 who did not recur could not. This mechanism was real but limited in size: three of the 54 OKC (6%), all recurrent and with the longest follow-up (11–23 years), had been operated on before 2015, whereas no OOC, retrieved from the same window, had a follow-up longer than 6 years, an asymmetry that is itself evidence of the selective entry of recurrent OKC. The sensitivity analysis restricted to the 51 OKC operated on in 2015 or later gave a recurrence rate of 72.5% (95% CI 58.3–84.1%) and a 5-year recurrence-free survival of 34.9%, only slightly lower than the full-cohort figures: the selective entry of prevalent cases therefore does not explain the high recurrence rate observed. Finally, the conservative group includes patients treated by decompression without a documented secondary enucleation, in whom a persisting lesion may have been recorded as a recurrence. Both the full-cohort and the incident-cohort figures should be regarded as real-world estimates from a referral setting rather than as the expected recurrence rate of OKC after adequate treatment.

The proportion of orthokeratinised lesions (52.2%) is far higher than the 10–15% reported in the literature [12,16–18] and than the 7% observed in a recent surgical series of 291 cases [31], and it varied widely between centres (from 18% to 70%; Table 5), a heterogeneity that, in the absence of a central slide review, may partly reflect differences in histological classification between pathology departments. The age profile of the cohort, with mean ages of 50.2 years in OKC and 44.1 years in OOC and a median of 45 years overall, is older than the classic second-to-third-decade peak of OKC [3,7,8] and is consistent with an adult referral population enriched in OOC, which typically presents in the third to fifth decades [12]. In this cohort, OOC recurred in 11.9% of cases; this value is higher than the 2–4% usually reported after enucleation [12,16] and is explained by the fact that three of the seven OOC recurrences followed decompression alone, without secondary enucleation, and by the shorter follow-up of this group (median 2 years), which limits the comparison; notably, all seven OOC recurrences were recorded in the Turin-area centres and none among the 42 OOC treated in Cuneo (Section 3.7). Importantly, the distinction between OKC and OOC emerged as the dominant prognostic factor (HR 5.76 in the Cox model

stratified by treatment group), confirming that keratinisation pattern, rather than being a predictor within a single disease, identifies two entities with different biological behaviour, as established by Crowley et al. (recurrence 42.6% versus 2.2%) [35] and incorporated in the current WHO classification [15,16].

4.2. Predictors of Recurrence Within OKC

Within the OKC group, none of the available clinical variables (age, sex, comorbidity, site) predicted recurrence in the binary comparison, whereas in the Cox model restricted to OKC (Table 2B), older age was associated with a slightly lower hazard of recurrence (HR 0.98 per year; $p = 0.033$), a borderline association with a confidence interval reaching 1.00, and lesion site and comorbidity were not independently associated with recurrence. The same tendency was present, without reaching significance, in the model for the whole cohort (Table 2A), whereas in the crude comparison of the whole cohort older age appeared to be associated with recurrence: these discrepancies illustrate how a binary recurred/not-recurred coding is confounded by the duration of observation and by the composition of the cohort when follow-up is variable, since the older patients with OKC include the prevalent cases with the longest observation. The direction of the association, with a higher hazard in younger patients, is in line with the predilection of recurrent and syndromic OKC for the first decades of life [21,22], but the estimate is imprecise and should be regarded as exploratory. The predictors identified by the literature, namely lesion size above 4 cm, multilocularity, cortical perforation, association with the dentition, daughter cysts and epithelial budding [33,34,36], were not available in our databases, and their absence is the main limitation of this part of the analysis. The recurrence risk stratification proposed by Titinchi on the basis of 2064 OKCs from 23 studies [34] relies precisely on these variables, and their prospective recording is a prerequisite for any future risk-adapted management strategy.

4.3. Adjuvant Therapies: Cryotherapy and 5-Fluorouracil

No recurrence was observed among the eight patients treated with excision plus adjuvant therapy. This finding should be interpreted with great caution. Five of the eight patients had an OOC and were treated with cryotherapy; given the low recurrence rate of OOC, their outcome is uninformative about the efficacy of the adjuvant. The remaining three patients had an OKC treated with topical 5-FU and were free of recurrence after 1, 3 and 5 years, a result that is consistent with the literature but rests on three patients. The median follow-up of the eight adjuvant patients was 2.5 years, barely longer than the median time to first recurrence of 2 years in this cohort, so that a large part of the recurrences expected in this group could not yet have been observed; moreover, the 95% confidence interval of a 0/8 recurrence rate extends to 37%, and that of a 0/3 rate to 71%, both compatible with the recurrence rates reported after enucleation alone. In addition, the comparison is unadjusted, treatment was not allocated at random, and lesion size, the main determinant of treatment selection, is unknown, so that confounding by indication cannot be excluded. Our data are therefore hypothesis-generating and cannot support the routine adoption of adjuvant therapy.

The rationale for adjuvant chemical or cryogenic agents applied to the bony cavity following enucleation is nonetheless well established. Stoelinga advocated Carnoy's solution in areas of soft tissue adherence combined with excision of the overlying mucosa, reporting markedly reduced recurrence rates [37]. However, concerns about the neurotoxicity of chloroform, a constituent of the original Carnoy's solution, prompted the development of modified formulations (MCS) and the exploration of alternative adjuvants, including cryotherapy and 5-FU. A systematic review by Winters et al. (2023) evaluated the safety

and efficacy of Carnoy's solution, MCS and 5-FU as adjunctive therapies in patients with non-syndromic OKC treated with enucleation and peripheral ostectomy: in the four studies included (62 patients), recurrences occurred only after MCS, and 5-FU combined the lowest recurrence with the fewest adverse events [38].

In the meta-analysis of Al-Moraissi et al., enucleation with liquid nitrogen cryotherapy was associated with a lower pooled recurrence rate (14.5%) than enucleation alone (23.1%) [25], whereas the systematic review of de Castro et al., restricted to conservative treatments, reported a 20.8% recurrence rate after enucleation alone and 11.9% when enucleation was preceded by decompression [39]. More recently, 5-FU has emerged as a promising alternative. A systematic review and meta-analysis by Singh et al. (2022) found no recurrences among 56 cases treated with topical 5-FU, noting a 20% rate of transient nerve paraesthesia, none of which was permanent [27]. A retrospective cohort study by Caminiti et al. (2021) further demonstrated a significantly lower recurrence risk with 5-FU compared with MCS (no recurrence in 34 patients treated with 5-FU versus 9 of 36 treated with MCS) [32]. Most recently, a 2024 systematic review and meta-analysis directly comparing 5-FU with MCS demonstrated that 5-FU was associated with a significantly lower recurrence rate and lower rates of permanent peripheral nerve injury [28], while a further systematic review and meta-analysis of 14 studies (282 lesions) reported no recurrences after 5-FU, compared with 24% after MCS, and described 5-FU as a promising adjunct pending adequately powered randomised trials [40]; the 5-FU protocol used in our centres (5% cream applied on gauze) differs from that of these studies only in the longer dwell time (5 days instead of 24 h). It should also be noted that the cryotherapy used in our centres relied on a hydrofluorocarbon-based cryogenic spray rather than on liquid nitrogen, whose depth of bone necrosis is better characterised, so that the evidence on cryotherapy summarised above does not directly apply to our five patients. In this context, the absence of recurrence in our 5-FU-treated OKC, although based on very few patients, is in line with the available evidence and supports the inclusion of 5-FU in prospective, adequately powered studies with standardised recording of lesion size and follow-up (Figures 3 and 4).

4.4. Surgical Approach and Confounding by Indication

In this series, the comparison of initial treatments was confined to the OKC group, because the treatment categories were unevenly distributed between histotypes (all five patients treated with cryotherapy and six of the ten patients treated conservatively had an OOC) and a pooled comparison would have been confounded by histotype, the dominant prognostic factor. Within OKC, the excision/non-excision dichotomy was not associated with recurrence in the time-to-event analysis (log-rank $p = 0.810$), and the four-category description identified a possible protective effect of adjuvant therapy and a high recurrence rate after conservative procedures, with the limitations discussed above. Because treatment violated the proportional hazards assumption in the whole-cohort model and because the adjuvant group had no events, treatment could be handled only as a stratification variable in the Cox model, so that no adjusted estimate of its effect is available, and the within-OKC comparison rests on only eight patients in the non-excision group. A retrospective series cannot separate the effect of treatment from the effect of case selection: small lesions are preferentially treated by enucleation alone, large or perforating lesions by decompression or by resection with reconstruction, and the 'conservative' and 'reconstructive' groups therefore represent opposite ends of the severity spectrum. The regrouping of procedures into four categories partly addresses the heterogeneity of the original 'other' group, which mixed marsupialisation and drainage with reconstructive procedures, but does not remove confounding by indication, and our data should not be read as evidence for or against any specific procedure.



(**a**)



(**b**)



(**c**)

Figure 3. (**a**) Intraoperative view: surgical exposure and incision of the keratocyst wall. (**b**) Application of topical 5-fluorouracil into the bony cavity after enucleation. (**c**) Closure of the surgical access.

The literature broadly confirms that treatment intensity is inversely related to recurrence risk. Al-Moraissi et al. reported pooled recurrence rates of 23.1% for enucleation alone, 17.4% for enucleation with curettage, 11.5% for enucleation with Carnoy's solution, 14.5% for enucleation with liquid nitrogen cryotherapy, 32.3% for marsupialization alone, 14.6% for decompression followed by residual cystectomy, and 8.4% for resection [25]. The two-stage approach of decompression followed by enucleation has been advocated for large lesions, as initial decompression induces cyst shrinkage, new bone formation and thickening of the cyst wall, facilitating safer and more complete secondary enucleation [29], although the meta-analysis of Al-Moraissi et al. (14 studies, 997 lesions) found fewer recurrences after initial enucleation with or without adjuvants (18.2%) than after decompression with or without secondary cystectomy (27.1%) [30]; in a recent 24-year series, marsupialization in selected cases was associated with a lower recurrence rate than

enucleation [31]. A large retrospective series of Chinese OKC patients reported by Fidele et al. further demonstrated that preservation of involved teeth combined with cortical perforation and the presence of daughter cysts were independent predictors of recurrence, highlighting the importance of wide surgical margins and, when necessary, extraction of associated dentition [36].

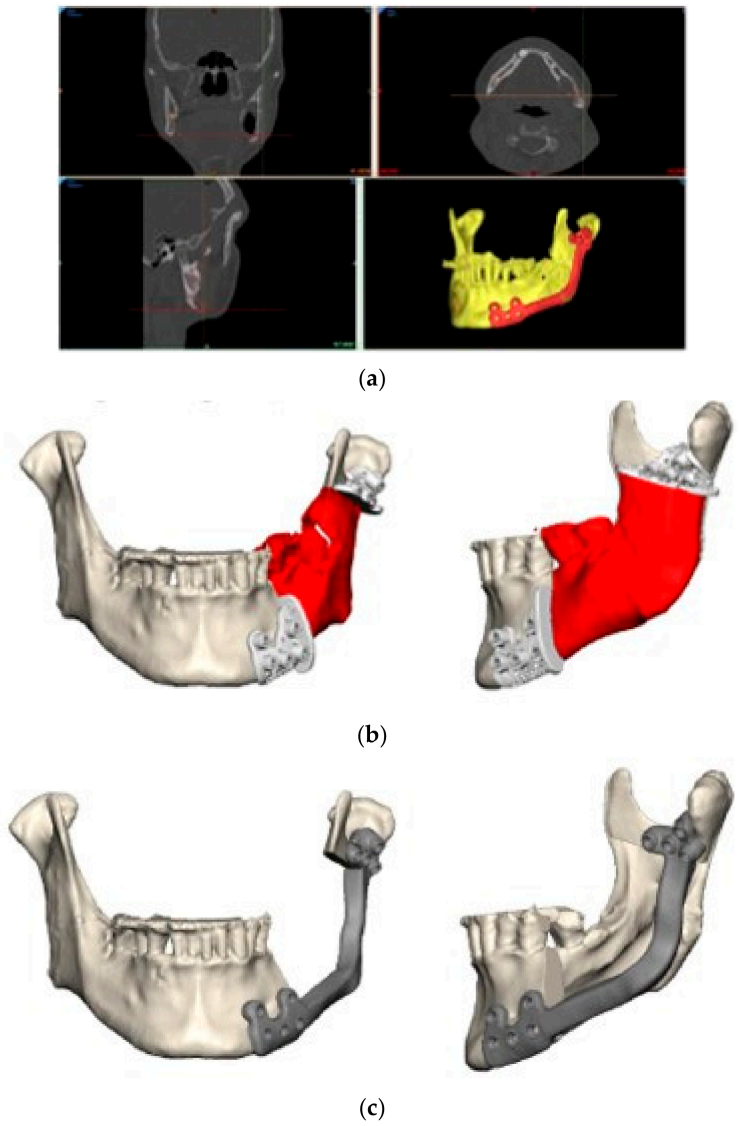


Figure 4. (**a**) Preoperative computed tomography of the keratocyst. (**b**) Virtual surgical planning of the bone resection with cutting guides. (**c**) Virtual surgical planning of the reconstruction with a customised prosthesis.

The balance between recurrence risk and morbidity calls for individualised treatment. Resection, while associated with the lowest recurrence rates, carries significant functional and aesthetic consequences and requires complex reconstructive procedures. For most patients with non-syndromic OKC, the current consensus favours enucleation combined with adjuvant therapy and peripheral ostectomy, as this approach achieves acceptable recurrence rates with limited morbidity [7,25].

4.5. Classification, Syndromic Status and Comorbidity

The recurring reclassification of OKC in successive WHO editions reflects the unresolved tension between its cystic morphology and its neoplastic behaviour. The 2005 WHO designation as keratocystic odontogenic tumour sought to translate its aggressive behaviour

and PTCH1 molecular profile into a neoplastic category, whereas the return to OKC in 2017 and 2022 was based on insufficient evidence for true neoplasia in sporadic cases, in which PTCH1 mutations were found in only 30–35% of lesions in some studies [13–17,19]. The same editions separated OOC as an independent entity, and the present data support this separation on clinical grounds.

The association between OKC and GGS deserves specific attention. OKCs are found in 74–80% of GGS patients, and syndromic cases carry recurrence rates of approximately 63%, probably because of a greater number of satellite cysts and epithelial rests [21,22]. In the present series only one patient (0.9%) had a diagnosis of GGS, an 18-year-old woman with a mandibular OKC treated by excision alone, who recurred after 2 years and was free of further recurrence after re-excision; this proportion is lower than in most published OKC series, probably because syndromic patients are followed in dedicated genetic and dermatological pathways, and no inference on the role of syndromic status is possible. Comorbidity, defined as the presence of a documented systemic disease, was more frequent in OKC than in OOC, in keeping with the older age of the former group and with the predominance of malignant, cardiovascular and metabolic conditions of adult life among the recorded diagnoses, but was not associated with recurrence in either the binary or the time-to-event analysis; it should not be read as a proxy for syndromic status.

4.6. Second and Third Recurrences and the Need for Long-Term Follow-Up

A second recurrence occurred in one-fifth of the patients who had recurred once, and a third in one-third of those who had recurred twice, with intervals of up to 12 years between successive events; all third recurrences occurred in OKC. With 9 and 3 events, respectively, regression models for second and third recurrences are not estimable in any meaningful sense; these outcomes are therefore reported as descriptive frequencies with their confidence intervals, which should not be interpreted as evidence that clinical or histological variables are unrelated to repeated recurrence.

The time-to-event analysis adds an element that binary recurrence rates cannot convey. The median time to first recurrence was 2 years, but 19% of first recurrences (all in OKC, up to 15 years after surgery) and all third recurrences were diagnosed more than 5 years after the previous operation, in agreement with Jung et al., in whose series of 266 patients one quarter of the recurrences were diagnosed more than 5 years after surgery and who recommended a minimum 10-year follow-up [9], and with Sánchez-Burgos et al., who reported disease-free intervals of up to 9 years and noted that recurrences have been described up to 10 years after treatment [41]. With a median follow-up of 4 years, and of only 2 years in OOC, the recurrence rates reported here are necessarily underestimates, and the degree of underestimation is not uniform across groups. Regular annual panoramic radiography, supplemented by cone-beam CT when clinically indicated, remains the standard of care for long-term monitoring; in our centres cross-sectional imaging was used during follow-up in about one third of patients.

4.7. Strengths and Limitations

This study has several strengths, including its multicenter design, the histological confirmation of all diagnoses and of all recurrences, the separate analysis of OKC and OOC in accordance with the current classification, the use of time-to-event methods that account for the variable duration of follow-up, and the quantification, through a sensitivity analysis restricted to the incident cohort, of the selection bias introduced by the retrieval window. The participation of four distinct centres in northwest Italy introduces real-world heterogeneity while allowing assessment of treatment across diverse clinical settings.

Limitations are substantial and must be acknowledged. The design is retrospective; treatment was not allocated at random, and surgical techniques varied across centres, so confounding by indication cannot be excluded, and treatment could be included in the multivariable model only as a stratification variable. Established predictors of recurrence, namely lesion size, locularity, cortical perforation, daughter cysts, soft-tissue extension and relation to the dentition, were not recorded; lesion size could not be retrieved from the stored imaging, and histological diagnoses were not centrally reviewed. Follow-up was short for a lesion known for late recurrence, and follow-up duration and time to recurrence were recorded in whole years rather than as exact dates: the time-to-event analyses therefore have a yearly resolution, event times are heavily tied, and the observation that no recurrence was recorded before 12 months cannot exclude that a recurrence diagnosed a few months before the first anniversary of surgery was recorded as 1 year. Six patients with a follow-up shorter than 12 months, five of whom belonged to the group of other initial treatments (a quarter of that group), could not be included in the time-to-event analyses; at the resolution of the recorded data, their exclusion did not change the estimates, but it further reduced the already small non-excision group. Although all centres adopted the same surveillance schedule, adherence to it could not be verified retrospectively; recurrences were defined by histological confirmation after re-intervention, so radiologically suspected lesions kept under observation would have been classified as non-recurrences, and a differential ascertainment between centres remains possible: the centre-level data (Table 5) show marked heterogeneity, with a proportion of OOC ranging from 18% to 70% across centres and all seven OOC recurrences in the three Turin-area centres versus none among the 42 OOC treated in Cuneo. In the absence of a central histological review, differences in the classification of keratinising cysts between pathology departments cannot be excluded and may contribute both to the high proportion of OOC and to the heterogeneity of OOC outcomes, so that the OOC comparison group should be interpreted with caution; the OKC recurrence rates (57.1% to 89.5%) did not differ significantly across centres ($p = 0.166$). The retrieval of patients from the surgical activity of a defined period over-represented recurrent cases whose primary operation preceded 2015; this selection bias has been quantified by the sensitivity analysis restricted to the incident cohort and proved small, and the incident-cohort estimates (72.5% recurrence and 34.9% 5-year recurrence-free survival in OKC) should be preferred when the results of this study are compared with the literature. The comparison of treatment groups is based on very small numbers, particularly for adjuvant therapy, and no adjustment for multiple comparisons was applied. Finally, with a single syndromic patient, the influence of GGS on recurrence could not be analysed.

5. Conclusions

The present multicenter retrospective study confirms that, once OOCs are analysed separately as required by the current WHO classification, OKC is a lesion with a very high propensity to recur: three-quarters of the OKC in this real-world series recurred, with an estimated 5-year recurrence-free survival of 37% (72.5% and 34.9%, respectively, in the incident cohort operated on from 2015 onwards), and the distinction between OKC and OOC was the only independent predictor of recurrence. Within OKC, initial treatment was not associated with recurrence-free survival; sex, comorbidity and site did not predict recurrence, and younger age was weakly associated with a higher hazard of recurrence. The absence of recurrence in the eight patients treated with excision plus adjuvant therapy, three of whom had an OKC treated with topical 5-fluorouracil, is consistent with the literature but is based on too few patients, too short a follow-up and an unadjusted comparison to support a change in standard management; it should be regarded as hypothesis-generating. These findings reinforce the importance of accurate histopathological subtyping at diagnosis,

of the prospective recording of lesion size and of the other established risk factors, and of long-term structured follow-up for all patients with OKC, given its well-documented propensity for late recurrence.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/app162110580/s1, Table S1: STROBE Statement—checklist of items that should be included in reports of cohort studies; Figure S1: flow diagram of patient selection. Ref. [42] is cited in Supplementary Materials.

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Informed Consent Statement: Because of the retrospective design and the use of anonymised data, individual informed consent for participation was not required under the regulations of the participating institutions. The intraoperative photographs shown in Figure 3 do not allow identification of the patient and, in accordance with the same regulations, no specific consent for their publication was required.

Data Availability Statement: The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

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