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## ORIGINAL ARTICLE

# Intralesional Infusion of Methotrexate as Neoadjuvant Therapy Improves the Cosmetic and Functional Results of Surgery to Treat Keratoacanthoma: Results of a Randomized Trial<sup>☆</sup>

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### KEYWORDS

Clinical trial;  
Methotrexate;  
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Surgery;  
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### Abstract

**Background:** Keratoacanthoma is currently considered to be an in situ squamous cell carcinoma that mainly affects patients over 70 years of age. The tumor has a good prognosis and, in some cases, can resolve spontaneously. Treatment involves simple excision. However, since the tumors generally occur on the face or extremities and display rapid growth, aggressive surgery may be required and the cosmetic results may be poor.

**Objective:** The primary study objective was assessment of the efficacy of presurgical intralesional methotrexate infiltration to reduce the size of the tumor and the corresponding surgical defect.

**Material and methods:** A prospective, randomized study was undertaken in patients with a diagnosis of keratoacanthoma of at least 1.5 cm who were seen in our service between January 2009 and January 2010. Two groups were established: one receiving a single infiltration of methotrexate prior to surgery and another that did not receive methotrexate.

**Results:** Of the 25 patients included in the study, 10 received neoadjuvant intralesional methotrexate (group A) and 15 underwent surgery without prior infiltration of methotrexate (group B). The patients in group A displayed a reduction of between 50% and 80% in the size of the lesion prior to surgery. No complications were observed either in relation to methotrexate infusion or surgery. In group B, only 1 patient had a slight reduction in the dimensions of the lesion prior to surgery. In the remaining cases, the lesions remained similar (4 cases, 26%) or had increased in size (10 cases, 66%) at the time of surgery. Five patients in this group required hospital admission following surgery.

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**PALABRAS CLAVE**

Ensayo clínico;  
Metotrexato;  
Queratoacantoma;  
Cirugía;  
Carcinoma  
epidermoide

**Conclusions:** Neoadjuvant intralesional methotrexate is well tolerated and reduces the need for aggressive surgery in elderly patients with keratoacanthoma measuring more than 1.5 cm on the face or extremities.

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### Ensayo clínico: la infiltración intralesional con metotrexato de forma neoadyuvante en la cirugía del queratoacantoma permite obtener mejores resultados estéticos y funcionales

#### Resumen

**Introducción:** El queratoacantoma es considerado hoy día un carcinoma epidermoide *in situ* que aparece principalmente en pacientes mayores de 70 años. Se trata de un tumor de buen pronóstico que, en algunos casos, muestra resolución espontánea.

El tratamiento de este tipo de tumoración es la exéresis simple. Sin embargo, la localización preferente en las regiones facial y acral, el tamaño y su rápido crecimiento son factores que hacen que la cirugía sea en algunos casos agresiva y antiestética.

**Objetivo:** El objetivo principal del estudio es evaluar la eficacia de la infiltración intralesional de metotrexato en la reducción del tamaño quirúrgico de la lesión y del correspondiente defecto quirúrgico resultante de la intervención.

**Material y métodos:** Se realizó un estudio prospectivo aleatorizado en el que se incluyeron todos aquellos pacientes atendidos en nuestro Servicio diagnosticados de queratoacantoma de al menos 1,5 cm de tamaño entre enero de 2009 y enero de 2010. Se establecieron dos grupos, uno en el que los pacientes recibieron una infiltración de metotrexato previamente al acto quirúrgico y otro en el que se realizó directamente la cirugía.

**Resultados:** De los 25 pacientes incluidos en el estudio, 10 casos recibieron neoadyuvancia con metotrexato intralesional (grupo A) y 15 casos fueron intervenidos mediante cirugía aislada (grupo B).

Los pacientes del grupo A mostraron una reducción en el tamaño tumoral en el momento de la cirugía que osciló entre un 50 y un 80%. Ninguno de los pacientes presentó complicaciones relacionadas con la inoculación del metotrexato ni con la intervención quirúrgica.

En el grupo B sólo uno de los casos mostró una discreta disminución de sus dimensiones en el momento del acto quirúrgico. El resto de las lesiones mostraron una estabilidad (4 casos; 26%) e incluso un aumento de las dimensiones del tumor (10 casos; 66%) en el momento de la intervención. Cinco de los casos incluidos en este último grupo requirieron ingreso hospitalario en relación con la intervención quirúrgica.

**Conclusiones:** El metotrexato intralesional como terapia neoadyuvante es una medida bien tolerada, que permite evitar cirugías agresivas en pacientes de edades avanzadas que presentan un queratoacantoma de diámetro superior a 1,5 cm localizado en la región facial y acral.

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## Introduction

Keratoacanthoma is a skin tumor that typically presents as a solitary lesion on the sun-exposed skin of elderly patients. It is clinically characterized by rapid growth, followed on occasions by a period of partial involution, and more rarely by a period of complete involution.<sup>1,2</sup> It has characteristic histologic features consisting of a keratin-filled crater surrounded by a proliferative atypical squamous epithelium. While there is sufficient evidence to suggest that keratoacanthoma is a clinically distinct variant of well-differentiated squamous cell carcinoma, this is still a subject of debate.<sup>1,2</sup>

Even though involution may occur in certain cases, the fact that keratoacanthoma has been classified as a well-differentiated squamous cell carcinoma with metastatic potential means that treatment must be definitive.

The current treatment of choice is surgical excision, using either conventional surgery<sup>1,2</sup> or Mohs micrographic

surgery with fresh tissue.<sup>3,4</sup> Alternative treatments are systemic retinoids,<sup>5</sup> radiotherapy,<sup>6,7</sup> curettage and electrodesiccation,<sup>8-10</sup> intralesional 5-fluorouracil,<sup>11-14</sup> and intralesional methotrexate.<sup>15-24</sup> Intralesional interferon alpha-2b<sup>25</sup> and topical imiquinoid<sup>26</sup> have also been used, but less frequently.

Keratoacanthoma is often located in areas in which surgical excision carries considerable risk in terms of functional or cosmetic impairment due to the size of the tumor.

The use of neoadjuvant therapy to reduce tumor size prior to surgery would thus simplify the procedure and offer better functional and cosmetic outcomes.

The main aim of the current study was to assess the efficacy of intralesional methotrexate to reduce the size of tumors prior to surgery and, therefore, also the size of the corresponding surgical defects. Secondary objectives were to assess the need for complex reconstruction procedures,

tolerance of methotrexate, and complications due to the administration of intralesional methotrexate.

## Material and Methods

We performed a prospective, single-center, double-blind, parallel study without placebo control. Included were patients diagnosed, both clinically and histologically, with keratoacanthoma at the Department of Dermatology of the Fundación Instituto Valenciano de Oncología in Valencia, Spain between January 1, 2009 and February 1, 2010.

## Inclusion Criteria

The inclusion criteria were as follows: a) age over 18 years, b) tumor location in the facial or acral regions, c) tumor size over 1.5 cm, and d) absence of liver, blood, or kidney disorders.

The study was approved by the hospital ethics committee and written informed consent was obtained from all participants.

## Study Groups

Patients were randomly assigned to 2 groups (A and B) at the baseline visit using sheets of paper stating A or B contained in sealed envelopes prepared by an observer not involved in the study. Patients in group A were treated with intralesional methotrexate and surgery and those in group B were treated with surgery only. All of the patients underwent surgery within 30 to 35 days of the baseline visit.

A case report form was completed for each patient to record key clinical and surgical information and any adverse events attributed to the administration of intralesional methotrexate. Photographs were also taken at the baseline visit and at the time of surgery to analyze changes in tumor size and appearance.

## Case Report Form

The case report form contained 4 sections. The first section was used to record the patient's personal details (age and sex), and the second to record the clinical features of the tumor at the baseline visit (time since onset, location, and size). A photograph was also taken of the tumor at this time.

The third section was used to record details of the administration of intralesional methotrexate. These included the volume of methotrexate required to completely change the color of the tumor to yellow and a record of whether or not the patient had experienced discomfort during the administration of the drug.

The fourth section was used to record surgical data, namely the size of the tumor (cm), the size of the surgical defect (cm), and the technique used to repair the defect (direct closure, flap, or graft). Photographs taken on the day of the operation to record the size of the lesion and the surgical defect were also included in this section.

## Study Variables

The main study outcome measure was the reduction in tumor size achieved with intralesional methotrexate. This was assessed on the basis of the information contained in the case report forms. Secondary measures were between-group differences in surgical defect size and the proportion of patients who required complex reconstruction procedures or hospitalization, or who experienced complications.

## Intralesional Administration of Methotrexate

### Laboratory Tests

All the patients in group A underwent a laboratory workup (complete blood count [CBC] and liver and kidney function tests) prior to the administration of methotrexate. The tests were repeated 7 days after administration to check for possible systemic complications.

### Material Used in Neoadjuvant Therapy

We administered a solution of injectable methotrexate supplied in 40-mL vials containing 1000 mg of the drug (25 mg/mL of methotrexate in an aqueous excipient solution of sodium chloride, sodium hydroxide, and hydrochloric acid). These vials are stable at room temperature and, if handled in aseptic conditions and protected from light, can be used for 3 years after opening.

The methotrexate was injected into the tumors using 5-mL syringes and 30-gauge needles.

### Injection Method

The methotrexate was injected into the base of the tumor until this acquired a yellowish color (Fig. 1).

### Assessment of Possible Adverse Effects Due to Intralesional Methotrexate

Adverse events due to the administration of intralesional methotrexate were recorded in the case report forms. We evaluated complications associated with the injection technique and with the drug. In the first case, we recorded whether or not the patient experienced discomfort during the injection and also noted any signs of necrosis or other local complications. The presence of possible systemic complications due to methotrexate was evaluated by laboratory tests (CBC, liver and kidney function tests, lipid profile, and urine sediment test).

### Assessment of Results and Statistical Analysis

The case report forms, which included photographic records, were evaluated by an external investigator who was not involved in the conduct of the study or the randomization of the patients to the treatment groups.

Because keratoacanthoma is a rare disease, rather than calculate a minimum sample size, we decided to recruit all patients diagnosed with keratoacanthoma within a specific period (January 2009 to February 2010).

Quantitative variables were compared using the *t* test and qualitative variables using contingency tables and the



**Figure 1** Eighty-year-old woman with a 4-month-old tumor that was histologically and clinically consistent with keratoacanthoma (patient 5, Table 1). A, 2.5-cm tumor on the back of the right hand. B, Tumor after treatment with intralesional methotrexate; note the yellow color. C, Tumor, now measuring 1 cm, at the time of surgery.

$\chi^2$  or Fisher test. Statistical significance was set at  $P < .05$ . The statistical analysis was carried out using SPSS version 15.0

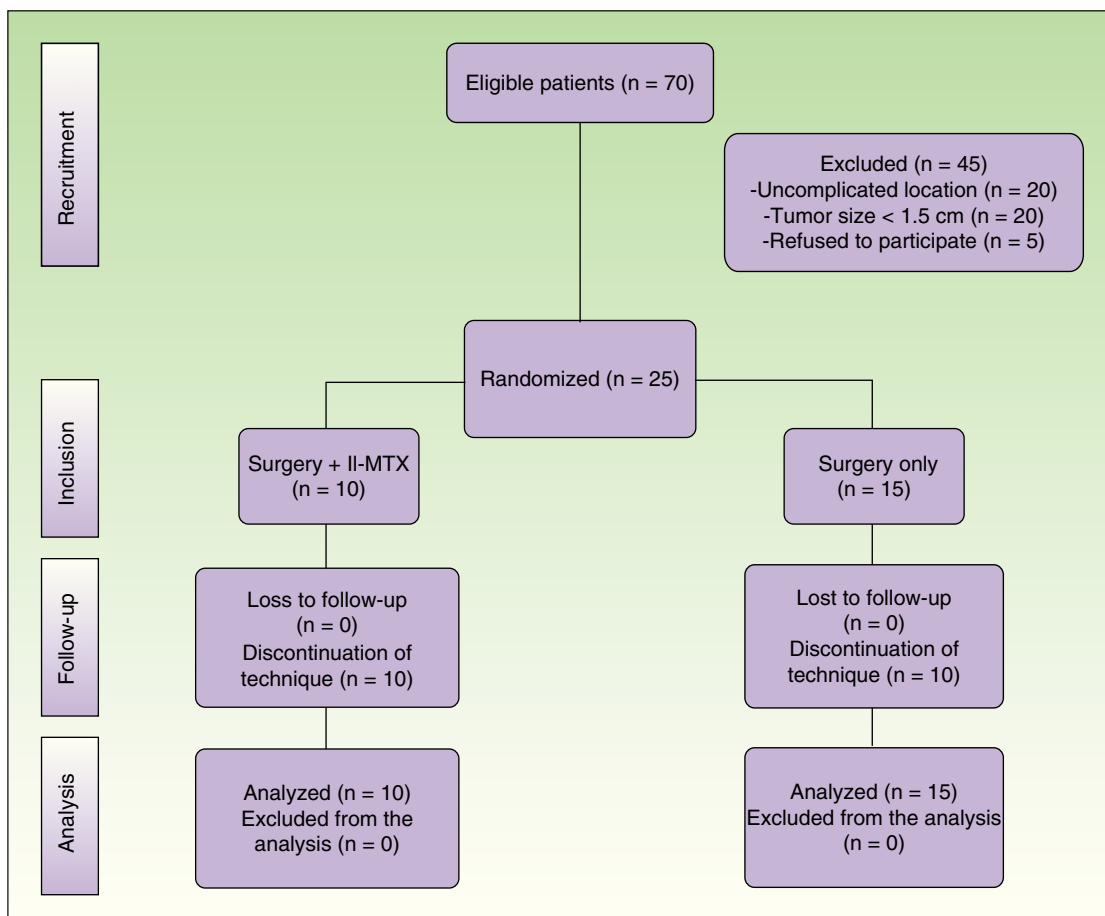
**Results**

Seventy patients were clinically and histologically diagnosed with keratoacanthoma during the study period. Of these, 25 (36%) met the inclusion criteria. The remaining 45 patients

were excluded because they had a tumor size of less than 1.5 cm (n = 20), because the tumor was not located in the facial or acral regions (n = 20), or because they refused to participate in the study (n = 5). (Fig. 2)

The 25 patients included were randomly allocated to group A (neoadjuvant intralesional methotrexate treatment group, n = 10) or group B (surgery-only group, n = 15).

The characteristics of the patients in each group are shown in Tables 1 (group A) and 2 (group B).



**Figure 2** Flow of patients throughout the trial. II-MTX indicates intralesional methotrexate.



**Figure 3** Seventy-year-old man with keratoacanthoma in the right infrapalpebral region; the tumor had appeared 4 months earlier (patient 2, Table 1). A, Tumor with a diameter of 2 cm at the baseline visit. B, Tumor, now measuring 1 cm, a month after neoadjuvant treatment with intralesional methotrexate.

The methotrexate group (Table 1) consisted of 5 men and 5 women with a mean age of 72 years. The mean time since appearance of the tumor in this group was 2.3 months. The lesion was located in the facial region in 7 patients (temple [n=4], periorcular region [n=2], and bridge of the nose [n=1]) and in the acral region (back of the hand) in 3 patients (Figs. 1, 3–5). The median tumor size was 2 cm (range, 1.5-2.5 cm). The median volume of intralesional methotrexate required for the tumors to acquire a yellow color was 0.5 mL (range, 0.3-0.5 mL). No complications were observed during the administration of the drug.

The surgery-only group (Table 2) consisted of 8 men and 7 women with a mean age of 70 years (range, 58-78 years) (Fig. 6). The median time since appearance of the tumor was 2 months (range, 1-4 months). The lesion was located in the facial region in 11 patients (cheek [n=5], temple [n=4], forehead [n=1], and bridge of the nose [n=1]) and in the acral region (back of the hand) in 4 patients. The median tumor size in this group was 2 cm (range, 1.5-2.7 cm).

The results of the between-group comparisons are shown in Table 3. No significant differences were detected in age, time since onset of tumor, or size of the tumor at the baseline visit. Tumor size, however, was significantly smaller in the methotrexate group than in the surgery-only group at the time of surgery (difference of 1.3 cm; 95% confidence interval [95% CI], 1.1-1.6 cm). The decrease in tumor size was 69% greater (95% CI, 62%-77%) in the methotrexate group than in the surgery-only group. The size of the surgical defect was also smaller in this group (mean of 1.45 cm less; 95% CI, 1.18-1.72 cm).

In a post-hoc analysis comparing the difference between the real size of the surgical defect and the estimated size (calculated using the initial tumor size and recommended surgical margins for cutaneous squamous cell carcinoma [4 mm for tumors <2 cm and 6 mm for tumors >2 cm]<sup>27</sup>, it was seen that the actual size was 1.53 cm smaller (95% CI,

**Table 1** Characteristics of Patients Treated With Intralesional Methotrexate (II-MTX) Before Surgery (Group A).

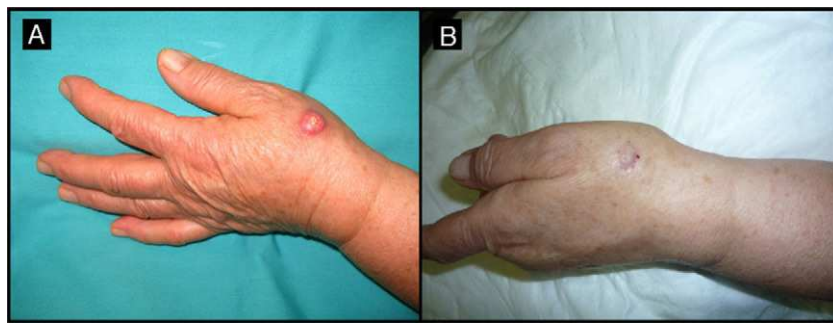
Patient/Age/Sex	Characteristics of Tumor at Baseline visit		Methotrexate		Characteristics of Tumor at Time of Surgery			Adverse Effects Due to II-MTX	
	Time Since Onset, mo	Location	Tumor Size, cm	Volume Injected, mL	Discomfort During Injection	Tumor Size, cm	Change in Size From Baseline Visit, cm		Size of Surgical Defect, cm
1/79/M	2	Left temple	2	0.5	No	0.4	-1.6 (-80%)	0.8	No/no
2/71/M (Fig. 3)	4	Right infrapalpebral region	2	0.5	No	1	-1 (50%)	1.5	No/no
3/52/F (Fig. 5)	3	Right eyebrow region	1.5	0.3	No	0.5	-1 (67%)	0.9	No/no
4/88/F	1	Right temple	1.7	0.3	No	0.8	-0.9 (53%)	1.2	No/no
5/80/F (Fig. 1)	4	Back of right hand	2.5	0.5	No	1	-1.5 (-60%)	1.5	No/no
6/66/F	2	Back of left hand	2	0.5	No	0.7	-1.3 (-65%)	1	No/no
7/70/M	2	Right bridge of nose	2.5	0.5	No	1	-1.5 (-60%)	1.5	No/no
8/72/M (Fig. 4)	1	Back of left hand	2	0.5	No	0.9	-1.1 (-55%)	1	No/no
9/75/F	2	Right temple	2.2	0.5	No	0.7	-1.5 (-68%)	1.1	No/no
10/65/F	2	Left temple	1.8	0.5	No	0.8	-1 (-55%)	1	No/no

Abbreviations: F, female; M, male.

**Table 2** Characteristics of Patients Treated With Surgery Only (Group B).

Patient/Age/Sex	Characteristics of Tumor at Baseline visit			Characteristics of Tumor at Time of Surgery				Hospitalization, Yes/No (d)
	Time Since Onset, mo	Location	Tumor Size, cm	Tumor Size, cm	Change in Size From Baseline visit, cm	Size of Surgical Defect, cm	Defect Closure Technique	
1/62/M	2	Left temple	2	2.2	+ 0.2 (+10%)	2.7	Direct	No
2/65/M	3	Forehead	2	2.3	+ 0.3 (+15%)	2.9	Flap	No
3/58/F	2	Back of left hand	1.5	2	+ 0.4 (+20%)	2.5	Direct	No
4/74/M	1	Right cheek	2.7	2.7	0 (0%)	3.3	Flap	Yes (2)
5/70/F	2	Left cheek	2	2.1	+ 0.1 (5%)	2.5	Direct	No
6/71/M (Fig. 6)	2	Right cheek	2.3	2.4	+ 0.1 (5%)	2.8	Flap	Yes (2)
7/70/M	2	Back of left hand	1.8	2	+ 0.2 (10%)	2.6	Direct	No
8/78/F	3	Left temple	2.2	2.4	+ 0.2 (10%)	2.9	Flap	Yes (2)
9/75/F	2	Right cheek	2.5	2.5	0 (0%)	3	Flap	Yes (2)
10/70/M	1	Left cheek	2	2	0 (0%)	2.4	Direct	No
11/71/M	2	Back of left hand	1.8	2	+ 0.2 (10%)	2.5	Direct	No
12/68/M	3	Right temple	1.8	2	+ 0.2 (10%)	2.5	Direct	No
13/59/F	3	Right bridge of nose	1.7	2	+ 0.3 (+15%)	2.4	Direct	No
14/65/F	2	Back of right hand	1.5	1.5	0 (0%)	2	Direct	No
15/67/F	4	Right temple	1.5	1.4	-0.1 (-10%)	2	Direct	Yes (1)

Abbreviations: F, female; M, male.



**Figure 4** Seventy-two-year-old man with keratoacanthoma on the back of his left hand (patient 8, Table 1). A, Tumor measuring 2 cm before intralesional injection of methotrexate. B, Tumor 1 month after treatment (65% reduction in size).

1.26-1.8 cm) in the methotrexate group than in the surgery-only group.

All the surgical defects in the methotrexate group were repaired using the direct closure technique. Furthermore, none of the patients in this group required hospitalization, experienced clinical complications, or had abnormal laboratory test results due to the administration

of intralesional methotrexate. In the surgery-only group, direct closure was possible in 10 patients and a skin flap was necessary in the other 5 patients. Five patients in this group also required hospitalization for 1 or 2 days.

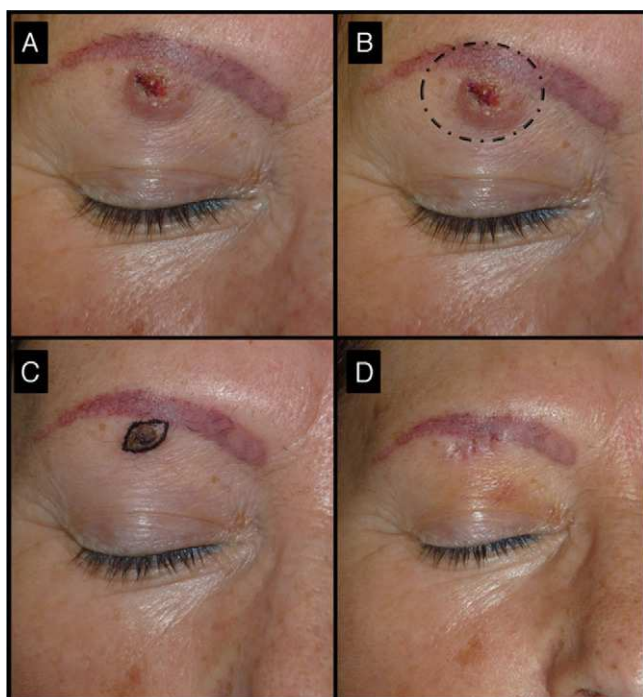
Histologic analysis of the surgical specimens showed typical features of keratoacanthoma. Of note in tumors treated

**Table 3** Comparison of Groups A and B Before Treatment and After Surgery.

	Group A (II-MTX+Surgery) (n = 10)	Group B (Surgery) (n = 15)	<i>P</i> <sup>a</sup>
<b>Before treatment</b>			
Sex			
Male	5	8	NS
Female	5	7	
Age, mean (SD) y	72 (10)	68 (6)	NS
Time since onset of tumor, mean (SD), mo	2.3 (1)	2.27(0.8)	NS
Initial size of tumor, mean (SD), cm	2.02 (0.32)	2 (0.36)	NS
Estimated size of surgical defect without neoadjuvant therapy, mean (SD), cm	2.94 (0.5)	2.86 (0.52)	NS
<b>After surgery</b>			
Change in size from baseline visit, mean (SD), cm	-1.24 (0.27)	0.15 (0.16)	<.0001
Percent change, mean	-61 (8.9)	8 (9.7)	<.0001
Estimated size of surgical defect without neoadjuvant therapy, mean (SD), cm	2.94 (0.5)	2.86 (0.52)	NS
Size of surgical defect, mean (SD), cm	1.15 (0.3)	2.6 (0.35)	<.0001
Hospitalization, No. of patients (%)	0/0%	5/33.3%	<.0001
Need for complex reconstruction during surgery, No. of patients (%)	0/0%	5/33.3%	<.0001

Abbreviations: II-MTX, intralesional methotrexate; NS, not significant.

<sup>a</sup> Calculated using the *t* test or  $\chi^2$  test to compare distribution between men and women.

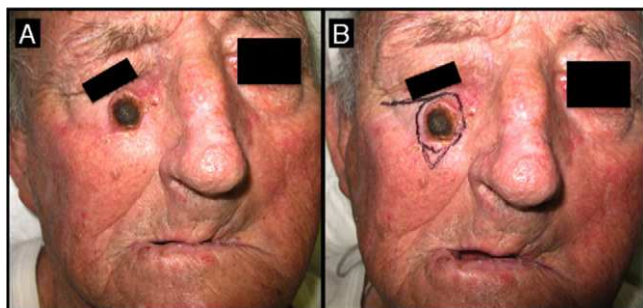


**Figure 5** Fifty-two-old man with keratoacanthoma of 3 months' duration under the right eyebrow (patient 3, Table 1). A, Tumor of 1.5 cm at the baseline visit. B, Surgical excision of a tumor of this size would have required cutting the eyebrow. C, Tumor, now a small papule measuring 0.5 cm, 1 month after treatment with intralesional methotrexate. The use of a small elliptical excision allowed the tumor to be removed without cutting the eyebrow, thereby achieving very good functional and cosmetic outcomes.

with intralesional methotrexate was a dense lymphocytic inflammatory infiltrate with a variable number of foreign body giant cells (Fig. 7).

## Discussion

Keratoacanthoma, which is also known as molluscum sebaceum, is a fast-growing skin tumor—possibly originating



**Figure 6** Seventy-one-year-old man with keratoacanthoma on his right cheek (patient 6, Table 2). A, Tumor with a diameter of 2.3 cm at the baseline visit. B, Tumor measuring 2.8 cm (not treated with intralesional methotrexate) at the time of surgery, 1 month later. An advancement flap was required to repair the surgical defect.

from the infundibulum of the hair follicle—that develops on sun-exposed skin.<sup>1,2</sup> Its classification has been a subject of debate as it has been described in the literature as a benign tumor, a pseudomalignant tumor, a malignant self-involuting tumor, and a subtype of squamous cell carcinoma.<sup>1,2,28–35</sup> These differences in proposed classification are explained by the fact that the clinical course of keratoacanthoma is both similar to and different from that of the variants of squamous cell carcinoma that have been described, with extremely rapid growth followed, in some cases, by partial regression.

Occasionally, keratoacanthoma can undergo complete spontaneous regression within a variable time period of a few months (generally 8 weeks).<sup>36,37</sup> Although there have been few cases reported, keratoacanthoma can also exhibit malignant behavior, with perineural invasion and even distant metastasis.<sup>28–35</sup> According to Hodak et al,<sup>29</sup> this justifies classifying this tumor as a squamous cell carcinoma with low metastatic potential. Sánchez Yus et al<sup>37</sup> and Weedon et al<sup>38</sup> consider that keratoacanthoma is similar to Bowen's disease in this respect, that is, it is a premalignant tumor with a risk of degenerating into squamous cell carcinoma in up to 25% of cases. Mandrell et al,<sup>36</sup> in contrast, consider keratoacanthoma to be a benign self-involuting tumor, and stated that the cases of metastasizing keratoacanthomas reported were probably diagnostic errors and were really squamous cell carcinomas.

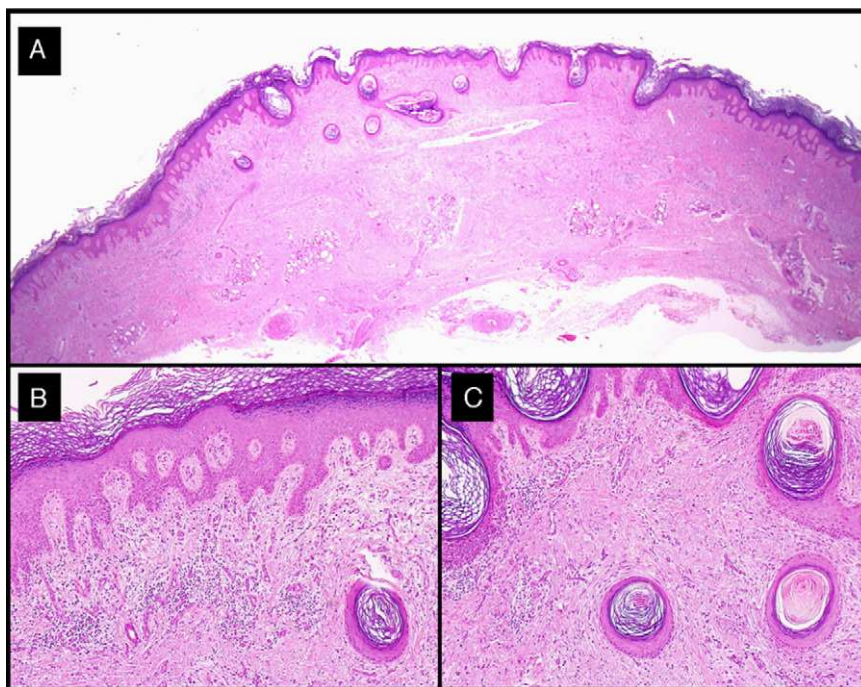
In our opinion, keratoacanthoma is a well-differentiated squamous cell carcinoma with low metastatic potential. The fact that most of the tumors in the surgery-only group in our study did not return seems to support this hypothesis. Indeed, 10 (66%) of the 15 tumors in this group increased in size in the 30 to 35 days between the baseline visit and surgery; the increase in size ranged from 5% to 20%. Four of the tumors remained stable and just 1 became smaller (reduction of 10%).

The treatment of choice for keratoacanthoma is complete surgical excision. This is for 2 reasons: first, in order to establish a definitive diagnosis, it is necessary to analyze the entire lesion to rule out foci of dermal invasion,<sup>36</sup> and second, if we assume that keratoacanthoma is a malignant subtype of squamous cell carcinoma, the most appropriate treatment according to the recently published National Comprehensive Cancer Network treatment guidelines is surgical excision with safety margins of 4 mm for tumors with a diameter of less than 2 cm and of 6 mm for larger tumors.<sup>37</sup>

The surgical removal of keratoacanthoma is associated with considerable morbidity, particularly in the case of large tumors (diameter of over 1.5 cm) and tumors located in the facial region (due to the risk of cosmetic and/or functional impairment) or on the back of the hands or feet (due to the risk of considerable functional impairment) (Fig. 5). In such cases, it may also be necessary to use flaps and/or grafts, leading to considerably lengthened surgery times and an increased risk of complications.

We have shown that the administration of neoadjuvant intralesional methotrexate in patients scheduled for surgical excision of keratoacanthoma and without contraindications for methotrexate can significantly decrease tumor size without interfering with routine dermatology practice. In our





**Figure 7** Histologic features of excised residual lesion after the administration of intralesional methotrexate (patient 3, Table 1). A-C, Dysplastic epidermis in association with a dense lymphohistiocytic infiltrate and some foreign body giant cells corresponding to the regression of the tumor following the administration of intralesional methotrexate (hematoxylin-eosin staining; original magnification: A,  $\times 10$ ; B,  $\times 40$ ; C,  $\times 100$ ).

study, a single injection of methotrexate 30 days before the operation led to a 50% to 80% reduction in tumor size (Figs. 1, 3–5). By contrast, only 1 of the tumors in the surgery-only group decreased in size, and the reduction was only slight; the rest stayed the same size or grew (Fig. 6). Intralesional methotrexate also led to a significant reduction in the size of the surgical defect (mean decrease of 1.45 cm). A post-hoc analysis based on estimated surgical defect sizes indicated that treatment with intralesional methotrexate reduced the size of the surgical defect by a mean of 1.7 cm. Finally, the neoadjuvant treatment also simplified surgery as all of the surgical defects in this group were repaired using direct closure. In the other group, 5 (30%) of the patients required a skin flap. One alternative to the use of intralesional methotrexate as neoadjuvant therapy in keratoacanthoma is 5-fluorouracil. We opted against this, however, for several reasons. 5-Fluorouracil requires local anesthetic as its injection causes intense pain. Furthermore, it needs to be administered weekly to achieve the desired effect (hence more visits to the dermatologist) and it causes necrosis of the tumor, complicating subsequent excision.<sup>11–14,24</sup> By contrast, based on the observations of our study, intralesional methotrexate can be administered in a single injection without local anesthetic and without causing necrosis, meaning its use will not increase the number of visits to the dermatologist or the waiting times for surgery (generally between 26 and 60 days).<sup>39</sup> The only disadvantage of intralesional methotrexate compared to 5-fluorouracil is that laboratory

tests are required to rule out blood, liver, or kidney disorders.<sup>15–24</sup>

While the current study has yielded interesting conclusions, it has several limitations. First, the fact that the treatment was not blinded might have led to a certain bias in that the results might have been interpreted as being more positive than they really were. To control for this, changes in tumor size and appearance were analyzed, using photographs, by observers not involved in the study. Second, a large proportion of patients diagnosed with keratoacanthoma were excluded from the study. This occurred because our intention was to include only patients who would truly benefit from the neoadjuvant therapy. This, combined with the fact that keratoacanthoma is not widely seen in routine clinical practice, means that relevant conclusions can be drawn from the results obtained. Nonetheless, it should not be forgotten that because of the small sample size, the study lacked statistical power to detect effects related to our secondary objectives, particularly adverse effects due to intralesional methotrexate. It should be noted, however, that the absence of adverse effects due to methotrexate in this study is consistent with data reported in the literature.<sup>24</sup> With respect to the risk of systemic effects of methotrexate, it should be noted that the maximum doses used in the current study correspond to systemic doses that are commonly administered in many diseases, including psoriasis in particular. Furthermore, intralesional methotrexate has been used, without complications, on previous occasions.

To conclude, given the simplicity of the technique and the lack of adverse events associated with its use in our study, the use of intralesional methotrexate should be considered prior to the surgical excision of keratoacanthomas with a diameter of over 1.5 cm, particularly in the case of tumors located in the facial and acral regions.

## Conflicts of Interest

The authors declare that they have no conflicts of interest.

## References

- Beham A, Regauer S, Soyer HP, Beham-Schmid C. Keratoacanthoma: a clinically distinct variant of well-differentiated squamous cell carcinoma. *Adv Anat Pathol.* 1998;5: 269–80.
- Manstein CH, Frauenhoffer CJ, Besden JE. Keratoacanthoma: is it a real entity? *Ann Plast Surg.* 1998;40: 469–72.
- Benest L, Kaplan RP, Salit R, Moy R. Keratoacanthoma centrifugum marginatum of the lower extremity treated with Mohs micrographic surgery. *J Am Acad Dermatol.* 1994;31: 501–2.
- Larson PO. Keratoacanthomas treated with Mohs' micrographic surgery (chemosurgery): a review of forty-three cases. *J Am Acad Dermatol.* 1987;16:1040–4.
- Wong WY, Kolbusz RV, Goldberg LH, Guana A. Treatment of a recurrent keratoacanthoma with oral isotretinoin. *Int J Dermatol.* 1994;33:579–83.
- Goldschmidt H, Sherwin WK. Radiation therapy of giant aggressive keratoacanthomas. *Arch Dermatol.* 1993;129: 1162–5.
- Caccialanza M, Sopolana N. Radiation therapy of keratoacanthomas: results in 55 patients. *Int J Radiat Oncol Biol Phys.* 1989;16:475–7.
- Reymann F. Treatment of keratoacanthomas with curettage. *Dermatologica.* 1997;155:90–6.
- Nedwich JA. Evaluation of curettage and electrodesiccation in treatment of keratoacanthoma. *Australas J Dermatol.* 1991;32:137–41.
- Sheridan AT, Dawber RP. Curettage, electrosurgery and skin cancer. *Australas J Dermatol.* 2000;41:19–30.
- Klein E, Milgram H, Traenkle HL. Tumors of the skin, II: keratoacanthoma, local effect of 5-fluorouracil (5-FU). *Skin.* 1962;1:153–6.
- Bergin DJ, Lapins NA, Deffer TA. Intralesional 5-fluorouracil for keratoacanthoma of the eyelid. *Ophthal Plast Reconstr Surg.* 1986;2:201–4.
- Parker CM, Hanke CW. Large keratoacanthomas in difficult locations treated with intralesional 5-fluorouracil. *J Am Acad Dermatol.* 1986;14:770–7.
- Thiele JJ, Ziemer M, Fuchs S, Elsner P. Combined 5-fluorouracil and Er:YAG laser treatment in a case of recurrent giant keratoacanthoma of the lower leg. *Dermatol Surg.* 2004;30: 1556–60.
- Melton JL, Nelson BR, Stough DB, Brown MD, Swanson NA, Johnson TM. Treatment of keratoacanthomas with intralesional methotrexate. *J Am Acad Dermatol.* 1991;25: 1017–23.
- Hurst LN, Gan BS. Intralesional methotrexate in keratoacanthoma of the nose. *Br J Plast Surg.* 1995;48:243–6.
- Cuesta-Romero C, de Grado-Pena J. Intralesional methotrexate in solitary keratoacanthoma. *Arch Dermatol.* 1998;134: 513–4.
- Remling R, Mempel M, Schnopp N, Abeck D, Ring J. Intralesional methotrexate injection: an effective time and cost saving therapy alternative in keratoacanthomas that are difficult to treat surgically. *Hautarzt.* 2000;51: 612–4.
- Spieth K, Gille J, Kaufmann R. Intralesional methotrexate as effective treatment in solitary giant keratoacanthoma of the lower lip. *Dermatology.* 2000;200: 317–9.
- Richard MA, Gachon J, Choux R, Laurans R, Folchetti G, Grob JJ. Treatment of keratoacanthoma with intralesional methotrexate injections. *Ann Dermatol Venereol.* 2000;127:1097.
- de Visscher JG, van der Wal KG, Blanken R, Willemsse F. Treatment of giant keratoacanthoma of the skin of the lower lip with intralesional methotrexate: a case report. *J Oral Maxillofac Surg.* 2002;60:93–5.
- Cohen PR, Schulze KE, Teller CF, Nelson BR. Intralesional methotrexate for keratoacanthoma of the nose. *Skinmed.* 2005;4:393–5.
- Annest NM, VanBeck MJ, Arpey CJ, Whitaker DC. Intralesional methotrexate treatment for keratoacanthoma tumors: A retrospective study and review of the literature. *J Am Acad Dermatol.* 2007;56:989–93.
- Good LM, Miller MD, High WA. Intralesional agents in the management of cutaneous malignancy: A review. *J Am Acad Dermatol.* 2011;64:413–22.
- Oh CK, Son HS, Lee JB, Jang HS, Kwon KS. Intralesional interferon alfa-2b treatment of keratoacanthomas. *J Am Acad Dermatol.* 2004;51:1040.
- Dendorfer M, Oppel T, Wollenberg A, Prinz JC. Topical treatment with imiquimod may induce regression of facial keratoacanthoma. *Eur J Dermatol.* 2003;13: 80–2.
- Brodland DG, Zitelli JA. Surgical margins for excision of primary cutaneous squamous cell carcinoma. *J Am Acad Dermatol.* 1992;27:241–8.
- Schwartz RA. The keratoacanthoma review. *J Surg Oncol.* 1979;12:305–17.
- Hodak E, Jones RE, Ackerman AB. Solitary keratoacanthomas a squamous cell carcinoma: three examples with metastases. *Am J Dermatopathol.* 1993;15:332–42.
- Mackie RH. Epidermal skin tumors. In: Champion RH, Burton JL, Ebling EJG, editors. *Textbook of dermatology.* 5th ed Oxford: Blackwell; 1992. p. 465–1470.
- Brenn T, McKee PH. Tumors of the surface epithelium. In: McKee PH, Calonje E, Granter SR, editors. *Pathology of the skin with clinical correlations.* 3rd ed London: Mosby Elsevier; 2005. p. 1221–6.
- Calonje E, Wilson Jones E. Intravascular spread of keratoacanthoma: challenges in management. *Dermatol Surg.* 1998;14:414–7.
- Cooper PH, Wolfe JT. Perioral keratoacanthoma with extensive perineural invasion and intravenous growth. *Arch Dermatol.* 1988;124:1341–97.
- Piscioli F, Zumiani G, Boi S, Cristofolini M. A gigantic, metastasizing keratoacanthoma: a report of a case and discussion on classification. *Am J Dermatopathol.* 1984;6: 123–9.
- Medalie NS. Keratoacanthoma with perineural invasion. *Australas J Dermatol.* 2002;43:155.
- Mandrell JC, Santa Cruz D. Keratoacanthoma: hyperplasia, benign neoplasm, or a type of squamous cell carcinoma? *Semin Diagn Pathol.* 2009;26:150–63.
- Sánchez Yus E, Simón P, Requena L, Ambrojo P, de Eusebio E. Solitary keratoacanthoma: a self-healing proliferation

- that frequently becomes malignant. *Am J Dermatopathol.* 2000;22:305–10.
38. Weedon DD, Malo J, Brooks D, Williamson R. Squamous Cell Carcinoma Arising in Keratoacanthoma: A Neglected Phenomenon in the Elderly. *Am J Dermatopathol.* 2010;32:423–6.
39. Ferrándiz L, Moreno-Ramírez D, Ruiz-de-Casas A, Nieto-García A, Moreno-Álvarez P, Galdeano R, et al. Teledermatología prequirúrgica en pacientes con cáncer cutáneo no melanoma. Evaluación económica. *Actas Dermosifiliogr.* 2008;99:795–802.