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Randomized comparative study in the treatment of oral leucoplakia with laser and conventional surgery

Estudo comparativo randomizado no tratamento da leucoplasia oral com laser e cirurgia convencional

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ABSTRACT

Objective: High-energy lasers are used as an alternative to surgical treatment of potentially malignant disorders in the oral cavity. The present article aims to make a prospective randomised comparative clinical assessment of the effect of laser surgery and conventional surgery in the treatment of oral leukoplakia (OL). **Material and methods:** In the study were included 89 patients with histologically confirmed oral leukoplakia lesions. Laser excision of the lesions using Er YAG laser was performed in 36 of the patients, while standard surgical excision was used in 53 of the cases. Following clinical assessment comparing the two treatment methods was conducted based on: pain, wound healing, infection and recurrence of the lesions. **Results:** A statistically significant difference between two groups according pain in the postoperative period was found. Patients treated with laser ablation experienced far less pain than those treated with surgical excision. The healing time was significantly faster in the group treated with Er YAG laser, and regarding the occurrence of postoperative infections, the results of the two methods did not differ significantly. Recurrence was observed earlier in the group treated with laser ablation, but the levels align over a longer period of time. **Conclusion:** Er YAG laser ablation is a contemporary method for the treatment of oral leukoplakia without dysplasia, providing similar success, compared to conventional surgical excision, with less postoperative discomfort for the patients.

KEYWORDS

Er YAG laser; Leukoplakia; Potentially malignant disorders.

RESUMO

Objetivo: Os lasers de alta potência são utilizados como alternativa ao tratamento cirúrgico de doenças potencialmente malignas da cavidade oral. O presente artigo tem como objetivo fazer uma avaliação clínica prospectiva e randomizada comparativa do efeito da cirurgia a laser e da cirurgia convencional no tratamento da leucoplasia oral (LO). **Material e Métodos:** No estudo foram incluídos 89 pacientes com lesões de leucoplasia oral confirmadas histologicamente. A excisão das lesões com laser Er YAG foi realizada em 36 dos pacientes, enquanto a excisão cirúrgica padrão foi utilizada em 53 dos casos. A avaliação clínica seguinte comparando os dois métodos de tratamento foi realizada com base em: dor, cicatrização da ferida, infecção e recorrência das lesões. **Resultados:** Foi encontrada diferença estatisticamente significante entre os dois grupos de acordo com a dor no pós-operatório. Os pacientes tratados com ablação a laser experimentaram muito menos dor do que aqueles tratados com excisão cirúrgica. O tempo de cicatrização foi significativamente mais rápido no grupo tratado com laser Er YAG e, em relação à ocorrência de infecções pós-operatórias, os resultados dos dois métodos não diferiram significativamente. A recorrência foi observada mais cedo no grupo tratado com ablação a laser, mas os níveis se alinham por um longo período de tempo. **Conclusão:** A ablação a laser Er YAG é um método contemporâneo para o tratamento da leucoplasia oral sem displasia, proporcionando sucesso semelhante ao da excisão cirúrgica convencional, com menor desconforto pós-operatório para os pacientes.

PALAVRAS-CHAVE

Laser Er YAG; Leucoplasia; Doenças potencialmente malignas.

INTRODUCTION

Potentially malignant oral disorders have rising tendency and the main reason for that are a number of exogenic and endogenic pathologic factors. Genetic damages of the epithelium accumulate in the process of carcinogenesis, leading to loss of ability to regulate the cell cycle and occurrence of uncontrolled propagation [1,2].

The World Health Organization has defined PMSD as clinical presentations that carry a risk of developing oral cancer, a clinically defined precursor lesion or clinically normal oral mucosa [3]. According WHO the most common PMODs with the highest potential for malignant transformation are leukoplakia, erythroplasia, oral lichen planus, actinic cheilitis and oral submucous fibrosis [1-3].

The specific causative factors of leukoplakia are still unknown; however, it is known that smoking/chewing tobacco as well as the alcohol abuse that would act synergistically with tobacco, trauma, electrogalvanic reactions, UV radiation, infestations as candidiasis, syphilis and human papillomavirus (HPV) are closely linked to the progression of leukoplakia [4-7].

Oral leukoplakia is the most common PMOD, presenting a prevalence of 1% and an annual malignant transformation risk of 2%. It affects equally men and women, rarely occurs in the first two decades of life. Approximately 70% of oral leukoplakia lesions are found on the buccal mucosa, vermilion border of the lower lip, and on gingiva [6-8].

Considering the macroscopic appearance leukoplakias are subdivided into homogeneous and nonhomogeneous. Homogeneous leukoplakias are characterized as uniformly flat and thin lesions with low percentage of malignant transformation, as well as spontaneous regression after elimination of risk factors, especially smoking habit. Nonhomogeneous leukoplakias are described as white and red lesions (erythroleukoplakias), which may appear irregularly flat or nodular, and are subdivided into a variety of subtypes, such as erythematous or speckled, nodular and verrucous [9, 10].

Pathohystological examination of leukoplakia can show hyperkeratosis, atrophy, acanthosis and may or may not demonstrate different degrees of epithelial dysplasia Dysplasia reflects histological changes which are followed by the loss of uniformity of the architecture of the epithelial cells.

According to these findings, oral leukoplakia can be distinguished as dysplastic and non-dysplastic lesions. Based on histological examination the presence of dysplasia has been associated with a risk of malignant transformation to oral cancer [2].

The diagnosis of OL is clinically confirmed by direct visual examination. Additional confirmation can be achieved by vital colouration with dyes, stomatoscopy and spectroscopy, and exfoliative cytology diagnostic testing. The histological examination of the biopsy specimens, combined immunohistochemistry, allows early registration of tissue alterations, before the clinical manifestation of the changes that have started on a cellular level [7,8].

The treatment of leukoplakia lesions include multiple treatment modalities such as surgical and conservative methods, this is why, the treatment plan is often individualized according to the histological findings, such as the degree of dysplasia found in the epithelium [8,9].

Regarding the prognosis of leukoplastic lesions, recurrence rates after any type of treatment can range from almost 0 to 30%, which means regular follow-up of patients every 6 months [8].

High-energy lasers are used as an alternative to surgical treatment.

The carbon dioxide (CO_2) lasers has a wavelength of 10 600 nm and is absorbed well by intra- and extracellular fluids. It produces rapid heating and evaporation of target tissues, causing a surrounding area of thermal necrosis. It is used with a focused wave for excision of the lesions, and defocused for evaporation [11-13].

Diode lasers are used in various modes of operation for the excision of the lesions.

The neodymium-doped yttrium aluminum garnet; Nd: $Y_3Al_5O_{12}$ (Nd YAG) laser has been used in medicine since 1973. It possesses powerful energy and penetrates deeply in the tissues. It is used for ablation of oral leukoplakia with very good outcome. A shortcoming of this laser treatment is the thermal effect causing pain during the procedure, requiring anaesthesia.

The use of erbium-doped yttrium aluminium garnet laser, erbium YAG laser (Er YAG) in oral surgery is highly efficient because of the high water absorption coefficient, compared with the CO_2 laser. The precise guiding and dosing of the laser beams allows the performance of lesion ablation without any coagulation effects in the surrounding tissues. Moreover they have shown low induction of inflammatory reactions and more rapid healing [4,9,14].

The purpose of this prospective, randomised study is to make comparative clinical assessment of the effect of laser and conventional surgery in the treatment of oral leukoplakia.

MATERIAL AND METHODS

Selection of the patients

The study was conducted at during the period September 2014 – December 2017, in the Medical University, Faculty of Dental Medicine – Plovdiv, Department of Maxillofacial Surgery, Department of Oral Surgery and St. George University Multiprofile Hospital for Active Treatment, Plovdiv, Bulgaria. During this period 89 patients, diagnosed with oral leukoplakia were subjected to conventional or laser surgical excision.

Inclusion and exclusion criteria

The inclusion criteria were a clinically verified diagnosis of OLs in 1st (size of OL lesion ≤ 20mm) and 2nd (size of OL lesion 20-40mm) stage with or without dysplasia and clear surgical margins on histological examination, signed informed consent from the patient. The diagnosis OL was set in accordance with the WHO criterion; as a "white plaque of questionable risk, (other) known diseases or disorders that carry no increased risk of cancers having been excluded [3].

Patients with pre-existing Oral squamous cell carcinoma (OSCC), or other cancer disorders, OL with severe dysplasia (high-grade intra-epithelial lesion, according to the 2014 Ljubljana classification), lesions, associated with local trauma or irritation and patients with other white lesions not identifiable as OL were excluded. In addition, surgical specimens with positive dysplastic margins and OSCC found in the first surgical specimen were excluded as well as patients with uncontrolled diabetes.

The 89 patients were randomly allocated in two groups: working group (WG) – 36 patients treated with laser ablation using Er YAG laser; and control group (CG) – 53 patients treated with surgical excision.

Informed consent was obtained from the patients at the Department of Maxillofacial Surgery, Medical University – Plovdiv, before the inclusion. The written consent was signed by the patient and the clinician that included the patient in the study. The study was approved by the Medical University of Plovdiv Ethics Committee and was conducted in accordance with the guidelines established in the Declaration of Helsinki.

Detailed history, including medical history, gender, age, medication, tobacco habits and alcohol habits as well as clinical examination and necessary investigations were performed in standard manner, for any patient included in the study. The items of clinical information registered were clinical diagnosis (homogeneous or non-homogeneous OL), localisation, lesion size, and multiple or single lesion.

Method of laser ablation procedure

The patients in the WG were treated with laser ablation method. OL lesions were ablated with Er:YAG laser (LiteTouch, Light Instruments, Israel) using "chisel" tip 0.6-0.8 mm at the following parameters: λ - 2940 nm, Energy - 200 mj, frequency 35Hz, and water spray level set at 10 mL/min. Topical anaesthesia with 10 per cent Lidocaine spray was used prior to the ablation. The treatment was performed in one session in contact mode as the entire area of the lesion in a particular location was subjected to ablation, reaching the surrounding healthy tissue. The underlying submucosa was reached in depth. The resulting wound surface was left on secondary healing. No suturing was used in working group owing to the better haemostatics property of the Er:YAG laser.

Surgical excision procedure

In accordance with the size of the lesions (L1 & L2) in the control group 53 patients were subject to complete surgical removal (excisional biopsy). Infiltration anaesthesia with 4% Articaine and Epinephrine 1/200000 was used for pain management. According to the official guidelines for excisional biopsy the OL was removed with a 3-5 mm clinical margin using conventional scalpel surgery [15]. Excision was followed by a primary closure or secondary healing in case of reduced mucosal defects or with a transposition of local mucosal flaps. Sutures were removed on the 7th postoperative day.

Histological examination - biopsies taken and transferred to the laboratory were fixed in 10% formalin solution for no more than 24 hours. The morphological diagnosis was made on tissue sections of 5 μm paraffin blocks, routinely stained with hematoxylin-eosin. Common cytological and histological criteria were used to establish dysplastic changes and their gradation.

The clinical follow up was performed on the 1st, 3rd and 7th postoperative days for both groups as well as on 3rd, 6th and 12th month.

The early postoperative indicators representing the process of healing of the surgical wound and the late indicator representing the effect of the method of treatment were evaluated.

Early indicators include: pain, infection and healing time.

• Pain: Evaluation for pain was done with the help of a Visual analog scale measured from 0 to 10, where 0 indicates absence of pain, 1-3 mild pain, 4-6 moderate pain, 7-10 severe pain [16].

• Infection – reporting the presence or absence of local signs of inflammation of the wound – redness, exudation, swelling, etc.).

• Healing time – assessment of the epithelisation of the wound on the 7th postoperative day. Registration of partial epithelisation, complete epithelisation and absence of epithelisation.

Late indicator –Recurrence was defined as the reappearance of an OL at the site of surgery [17]. The assessment was done in the 3rd, 6th and 12th postoperative month.

Statistical Analysis

MS Office 2010 and the **statistical software SPSS 2019** (IBM, International) was used for statistical **analysis**.

The frequency distribution was expressed in terms of number and percentage for categorical variables (each study parameter) to be compared among working and control group.

Chi-Square test was used to compare the distribution / association of the study variables between the three groups at each time interval. The mean and standard deviation (SD) was obtained for the pain scores and was compared between the groups using one-way ANOVA test followed by Tukey's HSD test as the Post hoc analysis. The level of significance (P-Value) was set at $p < 0.05$.

RESULTS

Study subject characteristics.

The study group comprised of 36% male and 64% female with average age of the patients 56.38 ± 0.97 years ranging from 34 to 80 years old. From the entire participant cohort, 35,9 % (n = 32) were smokers. The proportion of smokers in both tested groups was similar (p = 1.00). All patients from working and control group deny alcohol abuse.

The localization of oral leukoplakia was mainly on the buccal mucosa in both groups without statistically significant difference between male and female distribution. In male patients, lesions were located most commonly on the buccal mucosa (65,6%, n = 21), and in female patients on the buccal mucosa and attached gingiva (68.4%, n = 39) (p = 0.026). There were no differences in the location of lesions between the two tested groups (p = 0.17). Also the average size of lesions in both groups was similar.

Early postoperative indicators

Pain

Pain in the working and control group was compared on the day of surgery, third and seventh postoperative day using ANOVA test.

The data about pain intensity in patients from the working group are presented in Figure 1.

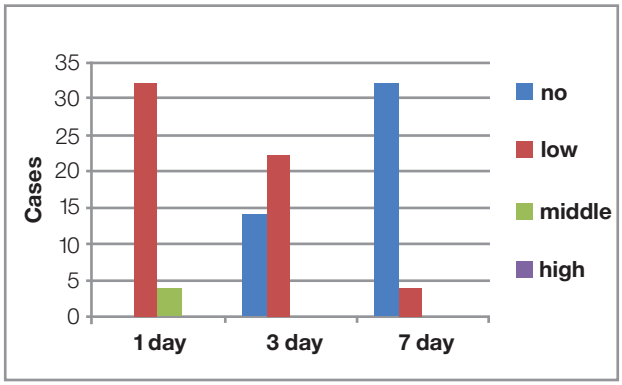

Figure 1 - Pain associated with ablation.

On the 1st day – 88.88% of the patients reported mild pain, 11.12% reported moderate pain.

On the 3rd day – in 38.88% of the patients pain was absent, and 61.12% reported mild pain.

On the 7th day – 88.88% of the patients were without pain, and 11.12% reported mild pain.

The data about pain intensity in patients from the control group are presented in Figure 2.

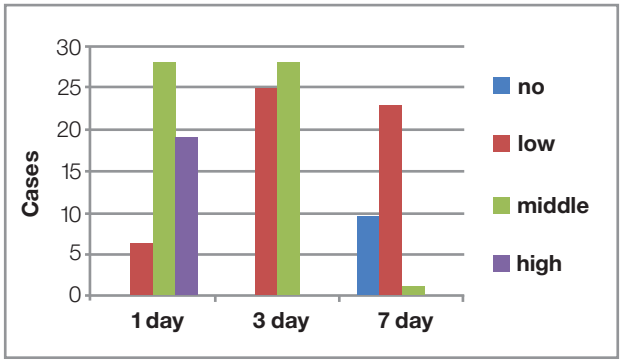

Figure 2 - Pain associated with excision.

On the 1st day – 11.3% of the patients reported mild pain, 52.8% reported moderate pain, 35.18% reported severe pain.

On the 3rd day – 47.2% of the patients were with mild pain, 52.8% with moderate pain.

On the 7th day – 30.2% of the patients were without pain, mild pain was present in 67.9%, 1.9% reported moderate pain.

The analysis reveals that the patients treated with laser ablation experienced statistically significantly less pain over the study period than the patient treated with surgical excision. The difference in pain intensity is statistically measurable - p=0.001.

Infection

One of the possible complications during the healing period of the surgical wound is the occurrence of infection. The results of the follow-up for presence of infection are presented in Figure 3.

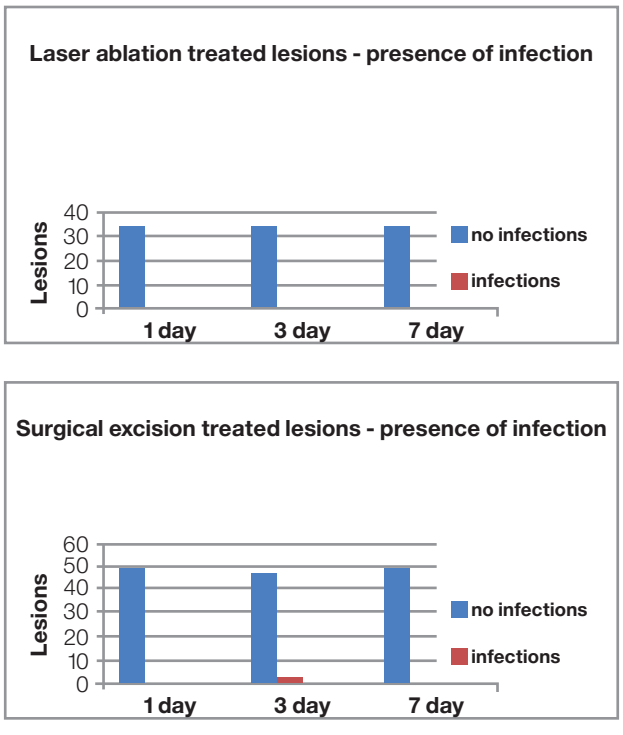

Figure 3 - Presence of infection.

Data analysis showed no infection in the working group treated with laser ablation over the study period. In the control group, treated with surgical excision, wound infection developed in the 3rd postoperative day in one patient (3.6%).

Healing

The data from for wound healing in working and control group is presented in Figure 4.

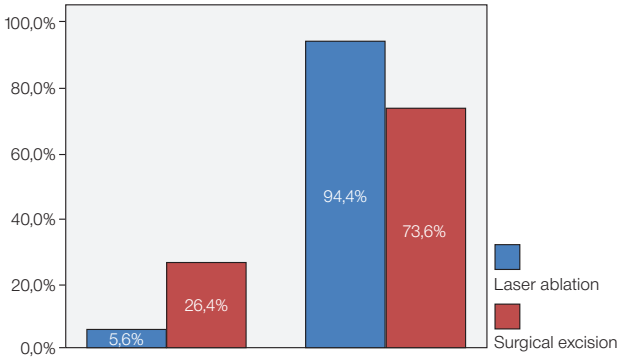

Figure 4 - Wound healing.

For the working group (laser ablation):

On the 7th day after the treatment 94.4% of the cases showed complete epithelisation. Partial epithelisation was observed in 5.6%.

For the control group (surgical excision)

On the 7th day after the treatment 73.6% of the wounds showed complete epithelisation, and 26.4% were with partial epithelisation.

The results of the study showed enhanced wound healing in the working group, treated with laser ablation.

Late postoperative indicators

Recurrence

Recurrence was defined as the reappearance of an OL at the site of surgery. On 3rd postoperative month in WG recurrence

was found in 13,9% of the cases, compared with 9,4% in the control group. On 6th postoperative month in WG recurrence was found in 16,7% of the cases, compared with 13,2% in the control group. On 12th postoperative month in WG recurrence was found in 22,2% of the cases, compared with 15,1% in the control group. The results of the study showed 25.8% recurrence rate after the treatment of OL over the entire study period (Figure 5).

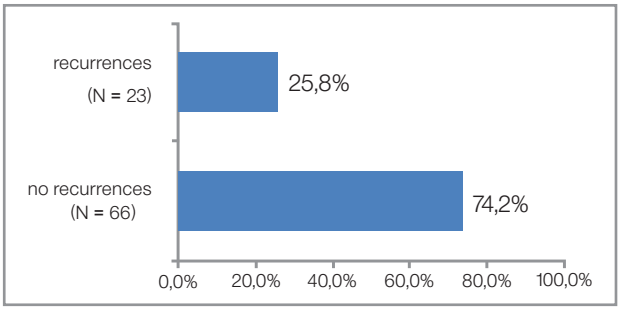

Figure 5 - Recurrence rate of OL.

The results of the recurrences found in the 3rd, 6th and 12th month in both groups are presented in Figure 6, Figure 7 and Figure 8.

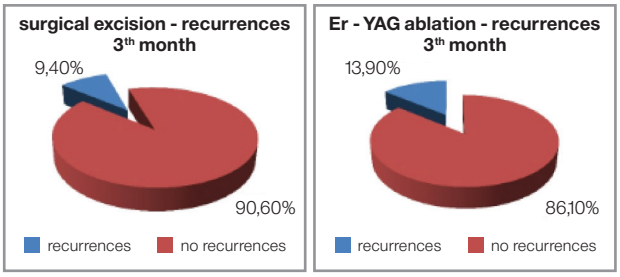

Figure 6 - Recurrence on the 3rd postoperative month.

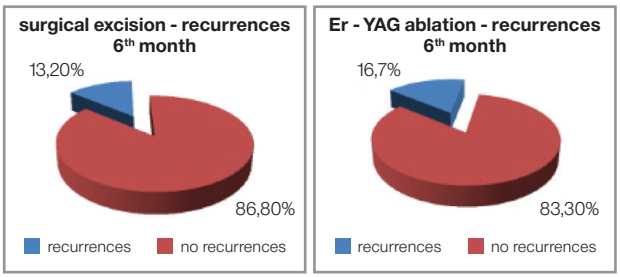

Figure 7 - Recurrence on the 6th postoperative month.

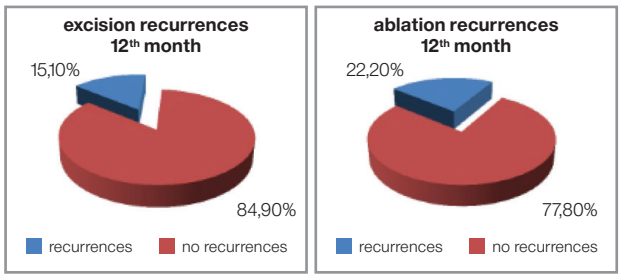

Figure 8 - Recurrence on the 12th postoperative month.

It has been found that after the third month, the percentage of recurrences following the treatment of OL with laser ablation increases minimally to the twelfth postoperative month. The percentage of recurrences after conventional surgical excision increase gradually, and by the twelfth postoperative month it reaches levels that are similar to those found in lesions treated with laser ablation.

No significant correlation was found between the two treatment methods and recurrence of OL.

DISCUSSION

The present study identifies important differences in the immediate postoperative period between the two treatments. On the first postoperative day, *mild pain* is reported from 88.88% in the WG, and 11.3% in CG. Severe pain is experienced by 35.18% in the CG of OL. On the third day, *lack of pain* is reported from 38.88% in the WG and 0% in CG. On the seventh day *lack of pain* is reported from 88.88% in the WG and 30.2% in CG. Significantly lower pain intensity in laser-treated patients is due to the atraumatic procedure, the lack of additional damage and thermal destructions in the surrounding tissues [1,2]. Furthermore, the laser can is believed to block the peripheral nerves at the wound and thus producing less pain in the post-operative period [18,19]. Similar low levels of pain with ablation of oral lesions using Er YAG laser have also been obtained by another author – Broccoletti R [12].

The cause for a more pronounced postoperative pain associated with the surgical excision is also related to the need of plastic closure of the defect. This leads to certain trauma for the surrounding tissues [4,15].

With regard to the inflammatory reaction, no singe case of infection developed in the WG. Isolated cases of wound infection were observed in the CG on the third day, which can be explained by the greater trauma of the from the cold blade surgery. The Er: YAG laser has a high sterilizing ability even when the output energy is low, and the temperature will not rise excessively. At the same time, the Er: YAG laser can split water molecules and produce OH-free radicals. A large number of oxygen free radicals also have certain bactericidal effects [19].

In terms of wound healing, we found faster healing in WG, as complete epithelization on the seventh day was observed in 94.4% of cases, comparing with 73.6% in CG.

This can be explained with the bactericidal and bio stimulation effects of the laser. By allowing the various growth factors involved in wound healing to work soon after the surgery, the less-than-profound hemostasis from the Er:YAG lasers compared with other intense coagulation, can be beneficial and, in many situations, preferable [13,14,18,19].

The analysis of the late indicator shows that recurrences are observed earlier in the working group, albeit the results equalize at the end of the study period. The presence of this process is most likely due to the fact that laser ablation only removes epithelium, whereas in the surgical excision tissues are removed in depth.

Vladimirov V. et al. [20] have found that giving up smoking significantly reduces the frequency of recurrences after surgical treatment of OL.

In our study we were unable to find differences in recurrence rate between OL with or without dysplasia, lesion size, sites of the lesions, alcohol consumption or smoking due to the similar distributions of these parameters between two groups.

CONCLUSION

The present study identifies important difference in the immediate postoperative surgical period between the two treatments, meaning that the Er:YAG laser seemed to be less painful, and better accepted by patients, than traditional scalpel. As many other authors like Broccoletti R et al. Ishii J et al. and Liu R et al. [12,18,19] we also found less postoperative pain, faster healing of the wounds and absence of inflammatory complications when laser ablation was used. When indicated, laser ablation performed with Er YAG laser provides opportunity to treat large-sized lesions where conventional cold blade surgery can not be easily performed.

The surgical treatment has always to be supported by histological analysis to identify the risk and consequently planning the clinical approach.

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Conflict of interest

The authors have no proprietary, financial, or other personal interest of any nature or kind in any product, service, and/or company that is presented in this article.

Regulatory Statement

This study was conducted in accordance with all the provisions of the local human subject's oversight committee guidelines and policies of the Medical University of Plovdiv, Bulgaria. The approval code for this study is N/ 00015269.

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