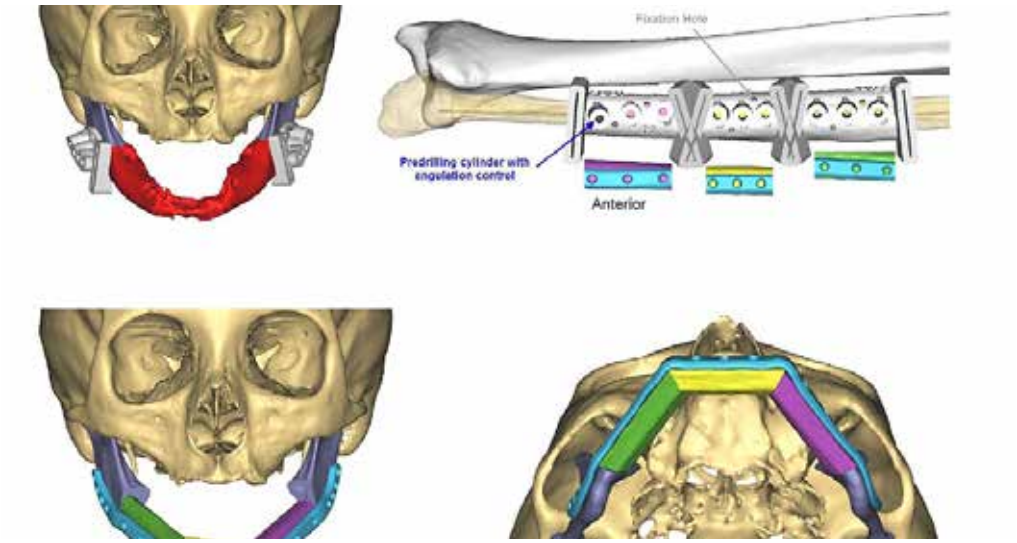
ACTA CHIRURGIAE PLASTICAE



Czakó et al., p. 145

Contents:

ČSPCH

Volume 63 | October 2021 | Issue 3

Published by the Czech Medical Association of J. E. Purkyně. ISSN (print) 0001-5423, ISSN (online) 1805-4404, Reg. No. E4844
ABSTRACTED/INDEXED BY: ADIS INTERNATIONAL LTD., EBSCOHOST, ELSEVIER BV (EMBASE, SCOPUS), INTERNATIONAL ATOMIC ENERGY AGENCY, PUBMED, MEDLINE, BIBLIOGRAPHIA MEDICA ČECHOSLOVACA

ACTA CHIRURGIAE PLASTICAE

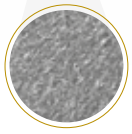
INTERNATIONAL JOURNAL OF PLASTIC SURGERY, MAXILLOFACIAL SURGERY, HAND SURGERY AND BURNS

Volume 63, No. 3, 2021

Contens

Motiva® 6th Generation Breast Implants[1]

The most comprehensive advanced smooth[2] portfolio with the only smooth ergonomic and smooth anatomical implants globally[3]



SmoothSilk®/ SilkSurface®

- Advanced **360° smooth surface** nanotechnology, bioengineered to be **cell friendly/biocompatible**[1,4]
- **Less bacteria and biofilm formation** compared to macro/microtextured surfaces[6,7]
- **Less inflammation and healthier capsule formation** compared to traditional smooth surfaces[8]

Less than 1% overall complication rate (capsular contracture, rupture, late seroma & double capsule)[9,10,11]

Of surgeons stated Motiva Implants® **reduce overall complications**[1]

FIRST-OF-ITS-KIND SAFETY FEATURES

TrueMonobloc®

Harmonious **shell-gel-patch** interaction designed to reduce rippling[5]

BluSeal®

100% visual confirmation of the gel barrier layer designed to minimize gel bleed[9]

Q Inside® Safety Technology

Optional **digital passport for implant traceability** (passive radiofrequency identification)[12]

ERGONOMIC GEL ProgressiveGel™ Ultima®

- Dynamic 'anatomical' implant designed to **mimic natural breast tissue** and **maximize patient comfort**[1]
- **100%** absolute consensus that the **Ergonomix® produces softer breasts** and **85% more natural look** compared to Motiva® Round implants[1]

STATE-OF-THE-ART MANUFACTURING

- **Energy-efficient and sustainable** Gold LEED* certified facility
- **MDSAP* certified** Quality System satisfying the strictest requirements of global regulatory jurisdictions including US FDA

EVOLUTION: Top 3 Reasons Surgeons Transitioned to Motiva Implants®[1]

92% Technology | 77% Implant softness | 62% Safety

1. Sforza M, Hammond DC, Botti G et al. Expert Consensus on the Use of a New Bioengineered, Cell-Friendly, Smooth Surface Breast Implant. Aesth Surg. J. 2019 May, 39(S3):S95-S102. doi: 10.1093/asj/sjz054 **2.** ISO-14607:2018 Non-active surgical implants - Mammary implants - Particular requirements. **3.** Atlan M. Lecture presented at: Audition publique ANSM.; March 26, 2019; Paris, France. **4.**Cappellano G, Ploner C, Lobenwein S et al. Immunophenotypic characterization of human T cells after in vitro exposure to different silicone breast implant surfaces. PLoS ONE 2018;13(2):e0192108. **5**. Chacón M, Chacón M, Fassero J. Six-Year Prospective Outcomes of Primary Breast Augmentation with Nano-Surface Implants. Aesthet Surg J. 2018; doi: 10.1093/asj/sjy196. **6.** James G, Boegli L, Hancock J et al. Bacterial Adhesion and Biofilm Formation on Textured Breast Implant Shell Materials. Aesth Plast Surg. 2019 Apr; 43:490–497. **7.** Jones P, Mempin M, Hu H, et al. The functional influence of breast implant outer shell morphology on bacterial attachment and growth. Plast Reconstr Surg. 2018;142(4):837-849. **8** Doloff J. Overcoming host rejection response to improve breast implant biocompatibility. Oral presentation at: 3rd World Symposium on Ergonomic Implants; Sep 2017; Lago di Garda, Italy. **9.** Sforza M, Zaccheddu R, Alleruzzo A et al. Preliminary 3-year evaluation of experience with SilkSurface and VelvetSurface Motiva silicone breast implants: a single-center experience with 5813 consecutive breast augmentation cases. Aesthet Surg J. 2018; 38(Suppl 2):S62-S73. **10.** Huemer GM, Wenny R, Aitzetmüller MM, Duscher D. Motiva Ergonomix Round SilkSurface Silicone Breast Implants: Outcome Analysis of 100 Primary Breast Augmentations over 3 Years and Technical Considerations. Plast Reconstr Surg. 2018; 141(6):831e-842e. **11.** Sim HB. Revisiting Prepectoral Breast Augmentation: Indications and Refinements, Aesthet Surg J. sjy294, https://doi.org/10.1093/asj/sjy294. **12.** Nelson MT, Brattain KA, Williams JM. Does Electronic Identification Enablement for Silicone Gel Implants Impact Patient Safety? J Surg Open Access. 2018;4(1). doi: 10.16966/2470-0991.162.

Product availability may differ by country, please check regulations for locally approved products.

*LEED = Leadership in Energy and Environmental Design, MDSAP = Medical Device Single Audit Program

www.motivaimplantaty.cz

Motiva® implants

20190409 V7

Editorial

Dear readers,
Despite the recent hot summer days and uncertain pandemic situation in Europe and over the world, the publishing activity of Acta Chirurgiae Plasticae is continuing permanently.

The face, and especially the maxillofacial region, is considered to be the dominant mark of a person. This idea rules both genders – male and female. For a woman, however, the breast region reveals to be of the same value, if not much more. Excellent esthetic results, such as minimizing scars and symmetry of reconstruction etc., contribute to the increasing level of the quality of life of our patients. Improving satisfaction with facial or breast region appearance, enhancing self-esteem, or lowering fear of negative appearance evaluation may enhance long-term psychological functioning.

As Prof. Ehrenfeld said: "Good results originate from experience, experience originates from bad results." Why to do it this way? Comparing own results with those from various other workplaces by PubMed, Web of Science, Scopus, Google Scholar etc. may help us in practical application of the principles of evidence-based medicine. A vast majority of research literature has suggested remarkable improvement in surgical outcomes under the guidance of 3D planning and computer-assisted navigation by better accuracy of surgery and shorter duration of the operation resulting in faster tissue healing, especially in microvascular free flap reconstructions.

Progress in the medical sciences is unbelievable and creates an increasing number of special groups of patients which were not obvious before, e. g. patients after solid organ transplantation. What would be the correct and optimal management of them?

You can find all these topics and, for sure, even more in the current issue of Acta Chirurgiae Plasticae you have now in your hands.

Have a nice reading!

Prof. Peter Stanko, MD, PhD

doi: 10.48095/ccachp202196

Fournier's gangrene secondary to male's circumcision – a case report and review of the literature

M. Tripoli, E. Cammarata, A. Cordova

Plastic and Reconstructive Surgery, Department of Surgical, Oncological and Oral Sciences, University of Palermo, Italy

Summary

Background: Fournier's gangrene is necrotizing fasciitis of the genitalia, perineal and perianal region associated with a significant mortality rate. The potentially fatal disease is caused both by aerobic and anaerobic bacteria and primarily occurs in men. The majority of Fournier's gangrene cases is idiopathic or derived from perineal and genital skin infections. Early surgical debridement of necrotic tissues and antibiotics are fundamental. **Case:** We report a rare case of Fournier's gangrene of a 57-year-old man secondary to circumcision. The patient presented due to painful swelling of the scrotum and perineum associated with high-grade fever. The patient received broad-spectrum antibiotics and underwent immediate surgical debridement; a total of five other debridements were performed during the recovery until the wounds healed. On a second recovery phase, we performed a penile reconstruction with full thickness skin graft with satisfactory cosmetic and functional results. **Conclusion:** FG remains an urgent condition associated with a high mortality rate, requiring immediate treatment. More statistical reports and standard guidelines are necessary to improve the rate of its survival.

Key words

Fournier's gangrene – necrotizing fasciitis – penile reconstruction – surgical debridement

Tripoli M., Cammarata E., Cordova A. Fournier's gangrene secondary to male's circumcision – a case report and review of the literature. Acta Chir Plast. 2021, 63(3): 96–101.

Introduction

The Fournier's gangrene (FG) was first reported in 1764 by Bauriene, who described a case of scrotal gangrene in a 45-year-old man, an army butcher, that was due to a traumatic injury in the genital region and the left thigh from the horn of an ox, 4 days before the clinical diagnosis. Bauriene stated that in cases of scrotal gangrene, radical surgical debridement of all infected and necrotic tissues is required. The testicles are not always affected, and in these cases, to safeguard the male reproductive system they must not be resected [1]. However, the disease was named after Jean-Alfred Fournier (1832–1914), a Parisian venereologist, who described a series of five otherwise healthy young men with a rapid gangrene of penis and scrotum without any apparent cause [2]. This disease is rare, rapidly progressing and potentially fatal necrotizing fasciitis caused by soft-tissue infections due to a mixture of aerobic and anaerobic microorganisms. Early recognition of the signs and symptoms is essential to prevent fatal consequences, and it consists of several aggressive surgical debridements of the necrotized tissue, several surgical irrigations, broad-spectrum intravenous antibiotics and early resuscitation.

Case

A 57-year-old man with a medical history of type 2 diabetes, treatment with metformin, 500 mg twice a day, presented to our emergency department due to pubic, scrotal and perineal swelling; the glans was sutured to the scrotal skin with nylon 4-0 stiches, the shaft was not visible, being covered with scrotal skin, and a purulent discharge was present from the balanopreputial sulcus (Fig. 1). The patient referred severe pubic pain and pyrexia with a temperature of 39.5 °C, which had started 3 days ago. Two weeks prior the presentation, he underwent a circumcision for recurrent balanoposthitis at an urology clinic external to the hospital. Following the operation, the patient described a fever resistant to the amoxicillin tablets (Fidia Farmaceutici, Italy) with a dose of 1 g twice a day administrated for 1 week, and worsening tenderness and induration of the scrotum. An urgent computer tomography (CT) scan revealed subcutaneous emphysema with a pubic, scrotal and perineal abscess. The laboratory analysis showed an increased white blood cell count ($18\times10^3/\mu L$) with neutrophilia and a higher C-reactive protein level (CRP); the sequential organ failure assessment (SOFA) score was 2, with < 33.3% mortality [3], while the FGSI (Fournier's

gangrene severity index) was 5, with the probability of survival 78% [4]. The patient was subsequently taken to the operative room urgently for scrotal and pubic exploration under general anaesthesia. Skin incision was performed along the scrotal raphe, abundant purulent fluid immediately flew out from the scrotum, revealing a necrotizing fasciitis involving the scrotal septum, cremaster and dartos muscles, tunica vaginalis of the right testis and epididymis (Fig. 2). The shaft of the penis was involved by pus and detached by the subcutaneous tissue. Several irrigations were performed with a mixture of saline solution and gentamicin sulphate antibiotic. After removing the scrotal abscess, full debridement of the necrotic fascia and subcutaneous tissue was performed; then the residual portion of the tunica vaginalis of the right testis was sutured by a running absorbable 3-0 suture, to avoid hydrocele. Another longitudinal pubic skin incision was performed, which exposed the abscess with necrosis of the Camper's fascia and Scarpa's fascia. After the purulent fluid removal and irrigation, a fistula was noticed between the pubis and the scrotum. All necrotic fatty tissue and the superficial fascia in the tunnel were excised. The culture obtained by the necrotic tissue showed an infection by *Staphyloccocus aureous* and *Escherichia coli*. An intravenous antibiotic treatment was administered with piperacillin/tazobactam (Mylan, Italy) in a dose of 4.5 mg 4times a day and levofloxacin (Fresenius Kabi Italia, Italy) 600 mg, twice a day; then, because of the appearance of an urticarial reaction, only linezolid (Fresenius Kabi Italia) was administrated orally in a dose of 600 mg twice a day, for other 2 weeks. The patient returned to the operating room for another surgical debridement after 2, 4, 8 and 16 days from the first operation until all nonviable necrotic tissue was excised. The patient was discharged from the hospital after 30 days from the first operation, once the wounds were

Fig. 1. Initial examination shows a pubic, scrotal and perineal abscess, and a periglandular purulent drainage.

Fig. 2. Fournier's gangrene in the patient during opening and draining the scrotum, the perianal area, the penis, and the anterior abdominal wall.

healed. After 3 months, the patient underwent a new surgery. Clinically, he presented a shortened penis with *corpora cavernosa* entirely covered by the skin of the scrotum (Fig. 3A, B). The procedure was performed under general anaesthesia. The glans was detached from the scrotum and debridement was performed to fully expose the *corpora cavernosa* surrounded by abundant scar tissue (Fig. 4). The suspensory ligament of the penis identified after removal of the fibrous tissue was stretched using the Z-plasty to increase the outward projection of the penis. Excess scrotal skin was removed and sutured to the root of the penis with 3-0 nylon stitches. Once the entire body of the penis was exposed, it was covered with a full thickness graft measuring 7 cm in width and 9 cm in length, taken from the abdominal fold and secured circumferentially to

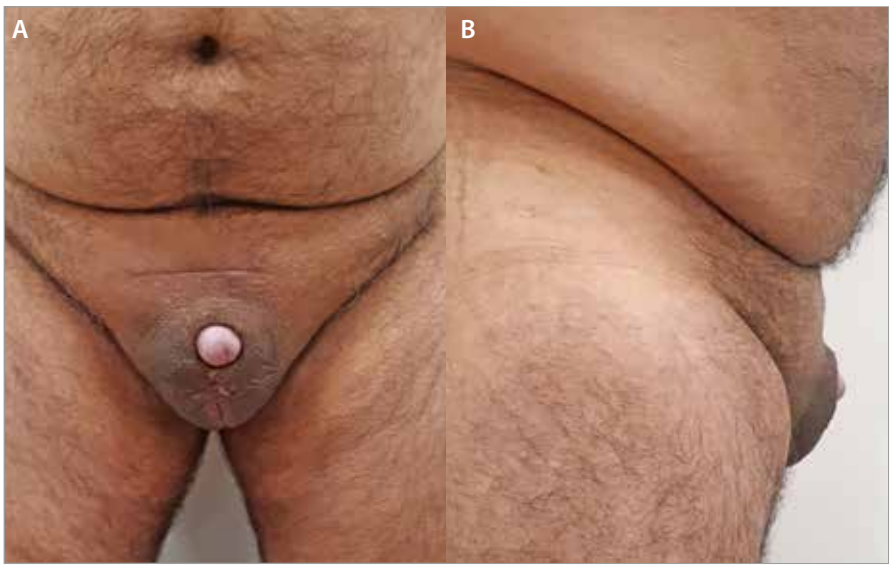


Fig. 3A, B. The patient after three months from the discharge: corpora cavernosa appear entirely covered by the skin of the scrotum.

Fig. 4. Degloving and debridement of the entire penis.

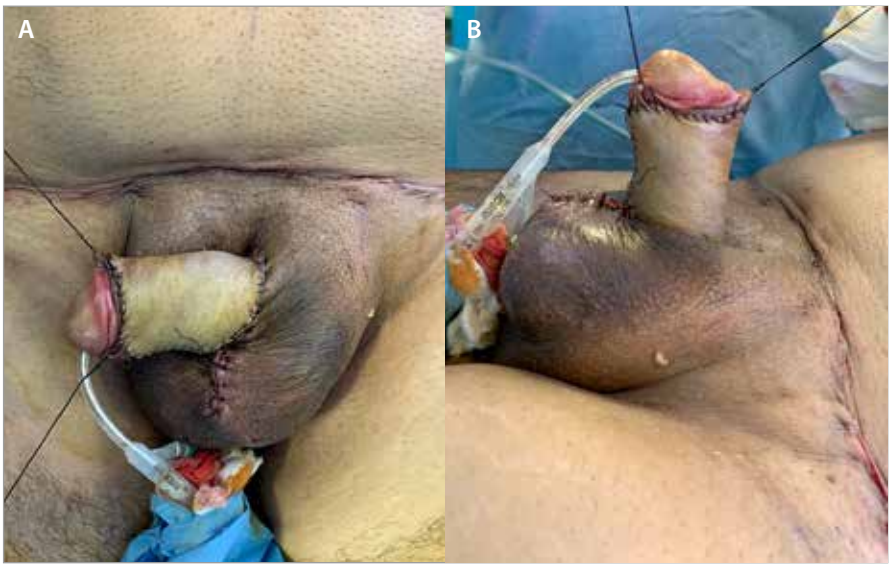


Fig. 5A, B. Placement of the full thickness skin graft harvested from the abdominal wall, ventral and dorsal view.

the body of the penis with a nylon 5-0 continuous suture (Fig. 5A, B). A bolster dressing was made to fix the graft to the recipient area.

After 5 days, the dressing was removed showing a graft take of 90%, a small necrotic area of the skin was surgically removed and left for healing by secondary intention. The patient returned home after 2 weeks. The patient resumed sexual activity after 2 months after the skin grafting. The aesthetic and functional result reported by the patient 1 year from the operation was very satisfactory (Fig. 6A, B).

Discussion

Fournier's gangrene represents a necrotic fasciitis of genitalia, perineum and abdominal wall, rapidly progressing and potentially fatal, due to soft tissue infection. It is rarely truly idiopathic; however, recent studies indicate that there is an underlying aetiology. Colorectal sources (30–50%), urogenital sources (20–40%), cutaneous infections (20%) and local trauma are frequently identified as the cause of FG [5]. Urogenital factors include an indwelling catheter, traumatic catheterization in case of longstanding urethral stricture, urethral calculi, prostatic biopsy, bladder carcinoma, epididymitis, balanitis, urinary extravasation, circumcision, vasectomy, insertion of penile prosthesis, penile erosion, tension-free vaginal tape procedure, hydrocele aspiration, delayed rupture of ileum neobladder, intracavernosal cocaine injection, and genital piercing, as well as perineal trauma and human bites or scratches as sexual trauma. Males are more affected than females with a ratio of 10:1, and the age of onset is becoming higher (60–70s) [6]. Metabolic disorders such as diabetes, alcohol abuse, human immunodeficiency virus and chronic steroid abuse are often associated with FG; these factors decrease the host immunity, allowing a portal of entry for aerobic and anaerobic microorganisms into the perineum, scrotum or penis, which start a rapid multiplication and spread of infection. Because of its rarity, most of the limited knowledge about FG derives from case reports and retrospective studies with small-size samples. In many cases, literature reports no identifiable source. These findings can be explained by the retrospective non-multicentre studies limitation,

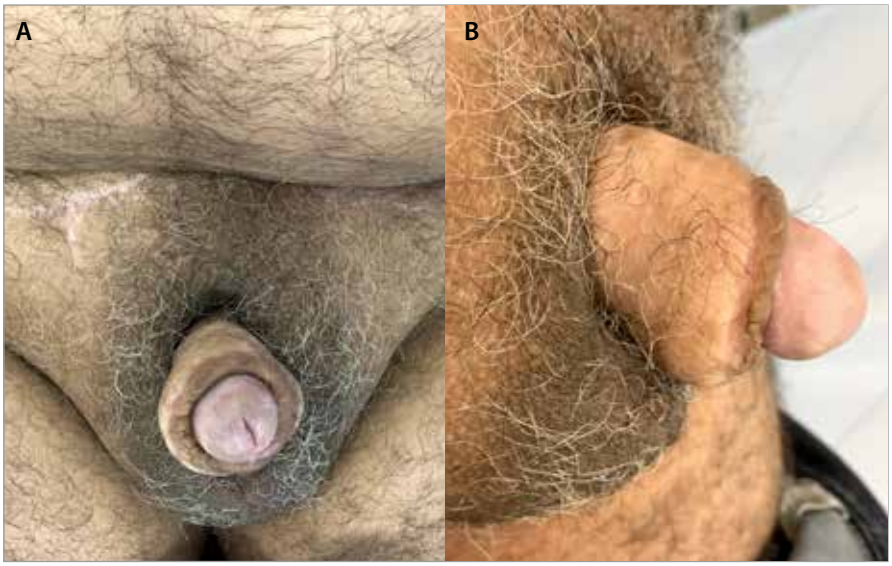


Fig. 6A, B. Result after 1 year from the surgery.

with a potential source of bias patients that were transferred to the plastic surgery department from other hospitals in advanced stage. According to literature, the most commonly isolated aerobic microorganisms include *Escherichia coli, Pseudomonas aeruginosa, Enterococcus faecalis, Klebsiella pneumonia, Streptococcus agalactiae*, and *Proteus*, while the most commonly isolated anaerobic microorganism are *Stafylococcus aureous* and *Bacteroides fragilis*. The mean number of debridement is 3.3 (range 1–4) [7].

The clinical features of FG include sudden scrotal pain and swelling associated with systemic features such as fever > 38 °C [8]. Purulent discharge and area of necrosis, acute renal impairment, anuria, poor hygienic conditions, and necrotic tissue involving the external genitalia are common associated conditions at the clinical examination [9].

The diagnosis of FG is primarily based on clinical findings. The infected area is swollen, dusky and covered with macerated skin and presents with a characteristic feculent odour, attributed to the role of anaerobes in the infection. Systemic signs may be pronounced, usually out of proportion to the local extent of the disease. In those with severe clinical presentation, progression of the gangrenous process to malodorous drainage and sloughing in affected sites results in the deterioration of patient's overall condition. Crepitus of the inflamed tissues is a common feature due to the presence of gas-forming organisms. As the subcutaneous inflammation worsens, necrosis and suppuration of subcutaneous tissues progresses to extensive necrosis. FG tends to spread along the fascial planes. Infection arising from the anal triangle can spread along the Colles fascia (superficial perineal fascia) and progresses anteriorly along the Dartos fascia to involve the scrotum and penis. It can also pass superiorly along the Scarpa fascia to involve the anterior abdominal wall. The Colles fascia is attached laterally to the pubic rami and fascia lata, and to the urogenital diaphragm posteriorly, thereby limiting the spread of infection in these directions. If the Colles fascia is interrupted, the infection can spread to the ischiorectal fossa and subsequently to the buttocks and thighs. Infection originating from the urogenital triangle, urethra, or periurethral glands can involve the Buck fascia, which initially limits infection to the ventral aspect of the penis. If the infection is not initially treated and the Buck fascia is penetrated, the infection may progress along the Colles and Dartos fasciae.

Patients can rapidly deteriorate as sepsis and multiorgan failure, the most common cause of death in these cases, develop [10]. FGSI is recommended to assess the mortality risk of FG. Described by Laor et al in 1995 [4], by modifying the acute physiology and chronic health evaluation scale to assign a numerical score to 9 parameters that predicted the severity and outcome of FG. FGSI was obtained by combining admission physiological (temperature, heart and respiratory rates) and laboratory parameters (white blood count, serum sodium, potassium, creatinine and venous bicarbonate). With FGSI > 9, the probability of death is 75%, and when the score is ≤ 9, the probability of survival is 78%. Other factors such as the duration of symptoms before hospital admission, extent of body surface area, number of surgical debridements, additional surgical manoeuvres (supra-pubic catheterization or colostomy), and microbiological cultures did not show significant differences [11].

Although the diagnosis of FG is most commonly made clinically, CT can be valuable in patients in whom the diagnosis is unclear or the extent of the disease is difficult to discern. CT has greater specificity for evaluating disease extent than does radiography or ultrasound (US). The CT features of FG include soft-tissue thickening and inflammation, asymmetric fascial thickening, fluid collection or abscess, fat stranding around the involved structures, and subcutaneous emphysema. Post treatment follow-up CT is valuable in assessing for the improvement or worsening of the disease to determine if additional therapy or surgery is needed. US is also useful in differentiating FG from inguinoscrotal incarcerated hernia; in the latter condition, gas is observed in the obstructed bowel lumen, away from the scrotal wall. US is superior to radiography since the scrotal content can be examined along with Doppler blood flow. Soft-tissue air is also more obvious at US than at radiography. Again, CT is superior to both US and radiography in demonstrating FG, its extent, and its underlying causes [12]. The management consists of urgent patient resuscitation, broad-spectrum antibiotic therapy, and surgical debridement. Parenteral broad-spectrum antibiotics are required, the therapy includes triple treatment with third-generation cephalosporins or aminoglycosides, penicillin and metronidazol and is adjusted according to the result of the cultures. In severe forms of the disease, antibiotics from the class of carbapenems are included in the complex processes of the antibacterial therapy [13]. Early surgical debridement is always recommended where necrotic tissue must be performed until the wound bed is clean. The use of adjunctive therapies such as hyperbaric oxygen therapy (HBOT) and vacuum assisted closure are supported in some aspects of the literature and disputed in others. HBOT has bactericide and bacteriostatic effects on anaerobic pathogens; in particular, it also improves bacterial lysis by leukocytes and stimulates collagen formation and superoxide dismutase with tissue survival. Some authors have reported a lower range of mortality for the patients who undergo HBOT, approx. 17.6 vs. 16–30% without HBOT [14].

Once the infection has been treated, there is a necessity of the reconstruction of the surgical wounds with the best functional and cosmetic results

and minimal morbidity possible. The options include healing by secondary intention, primary closure or reconstructive procedures with skin grafts or flaps. The skin grafting is the most popular surgical option; its advantages include a simple one-stage procedure and low donor site morbidity as well as the possibility to cover large areas with reasonable functional and cosmetic results [15]. Donor areas also include the abdominal inferior fold, inguinal fold for full thickness skin graft, anterior aspect of the thigh and scrotum for split thickness skin graft; however, this technique should only be performed in case of healthy scrotal wound bed or chronic scrotal pain. Discomfort is often reported in case of using this area. The scar contraction of the graft could be problematic and may limit reconstruction of larger defects. There is also a risk of graft loss due to hematoma, shearing or infection. Full thickness skin graft is often used in penile reconstruction for its minimal contraction compared to thin skin grafts and it does not appear to interfere with sexual and erectile function. Perineal and perianal areas often present reconstructive challenges due to the risk of faecal and urine contamination, tissue maceration and trauma. For this reason, the reconstruction with split-thickness skin grafts is frequently impaired, making them useful options for small defects only [16–17].

Flap reconstruction has been reported for covering defects larger than half the area of the scrotum or extending beyond it. It has been reported in early stage reconstruction and represent an ideal option to cover the testes [18]. The flaps provide more durable protection, without relying on granulation tissue. These procedures are technically more complex and require a longer surgery time and they are associated with higher morbidity. Local advancement flaps, myocutaneous and fasciocutaneous flaps are often described. Scrotal flaps are an ideal option for small defect reconstruction, with low donor site morbidity and significant aesthetic results. They can also be used for penile and perineal reconstruction due to the scrotal skin extensibility [19]. Among fasciocutaneous type flaps, the medial thigh flap is frequently harvested for the scrotal reconstruction. Described by Hallock [20], it is based on the communicating suprafascial vascular plexus of the medial thigh. With its dimension of up to 9 × 20 cm, it provides a good aesthetic result with primary donor site closure. The anterolateral thigh flap is an ideal option for medium and large perineal, penile, anal and scrotal defects. The flap is based on the descending branch of the lateral femoral circumflex artery; the pliability of the tissue, the primary closure of the donor site, and the satisfactory aesthetic results are the main advantages of this type of reconstruction. In case of extensive defects, a pedicled deep inferior epigastric perforator is indicated, although its indications in male genital reconstruction are limited by its bulkiness [21]. In case of urethral defects, usually a full-thickness skin graft or an oral mucosa graft is considered.

Conclusion

FG is an urological emergency with a high mortality rate despite advances in the medical and surgical fields. The early recognition and immediate surgical intervention appears mandatory to face the aggressive nature of the infection. It requires a high clinical level of suspicion, combined with the knowledge of anatomy, risk factors, and aetiology for an accurate diagnosis. Although FG remains a clinical diagnosis, relevant laboratory and radiography investigations can serve as useful adjuncts to expedite surgical management, hemodynamic resuscitation, and antibiotic administration [22].

The gold standard of treatment seems to be the triad: intravenous fluid resuscitation, emergency surgical debridement, and broad-spectrum intravenous antibiotics [23]. The individual characteristics of the defect, patient preference and surgeon experience must be considered to choose the ideal option of reconstruction, which includes technically rapid and simple procedures such as skin grafting with lower donor site morbidity, associated, however, with less satisfactory aesthetic results, fasciocutaneous or perforatos flaps, which probably provide better testicular protection with lower incidence of contracture and higher quality of cover. These surgical procedures are technically more complex, and they are associated with higher donor-site morbidity; furthermore, due to its bulkiness, other operations could be necessary to improve the aesthetic results [24]. FG remains an urgent condition associated with a high mortality rate, requiring immediate treatment. More statistical reports and standard guidelines are necessary to improve the rate of survival.

Roles of authors: All authors have been actively involved in the planning, preparation, analysis and interpretation of the findings, enactment and processing of the article with the same contribution.

Disclosure: The authors declare there are no conflicts of interest regarding the publication of this article. The authors declare that this study has received no financial support. All procedures performed in this case were in accordance with ethical standards of the institutional and/or national research committee and with the Helsinki declaration and its later amendments or comparable ethical standards.

References

1. Bauriene H. Sur une plaie qui s'est terminee par la sphacele de la scrotum. *J Méd Chir Pharm.* 1764, 20: 251–256.

2. Fournier JA. Gangrene foudroyante de la verge. *Sem Méd.* 1883, 4: 589–597.

3. Vincent JL., Moreno R., Takala J., et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med.* 1996, 22(7): 707–710.

4. Laor E., Palmer LS., Tolia BM., et al. Outcome prediction in patients with Fournier's gangrene. *J Urol.* 1995, 154(1): 89–92.

5. Moussa M., Chakra MA. Isolated Penile Fournier's gangrene: a case report and literature review. *Int J Surg Case Rep*. 2019, 62: 65–68.
6. Obi AO. Isolated Fournier's gangrene of the penis. *Niger J Clin Pract*. 2016, 19(3): 426–430.
7. Louro JM., Albano M., Baltazar J., et al. Fournier's gangrene: 10-year experience of a Plastic Surgery and Burns Department at a Terziary Hospital. *Acta Med Port*. 2019, 32(5): 368–374.
8. Kuzaka B., Wróblewska MM., Borkowski T., et al. Fournier's gangrene: clinical presentation of 13 cases. *Med Sci Monit*. 2018, 24: 548–555.
9. De Zingaro M., Boni A., Rossi De Varmondois JA., et al. Fournier's gangrene and intravenous drug abuse: an unusual case report and review of the literature. *Open Med (Wars)*. 2019, 14: 694–710.
10. Chennamsetty A., Khourdaji I., Burks F., et al. Contemporary diagnosis and management of Fournier's gangrene. *Ther Adv Urol*. 2015, 7(4): 203–215.11. García MA., Martín GJ., Vaquero RA., et al. Fournier's gangrene: analysis of prognostic variables in 34 patients. *Eur J Trauma Emerg Surg*. 2015, 37(2): 141–145.
12. Gupta N., Zinn MK., Bansal I., et al. Fournier's gangrene: ultrasound or computed tomography? *Med Ultrason*. 2014, 16(4): 389–390.
13. Chernyadyev SA., Ufimtseva MA., Vishnevskaya IF., et al. Fournier's gangrene: literature review and clinical cases. *Urol Int*. 2018, 101(1): 91–97.
14. Rosa I., Guerreiro F. Hyperbaric oxygen therapy for the treatment of Fournier's gangrene: a review of 34 cases. *Acta Med Port*. 2015, 28(5): 619–623.
15. Karian LS., Chung SY., Lee ES. Reconstruction of defects after Fournier gangrene: a systematic review. *Eplasty*. 2015, 15: e18.
16. Ferreira PC., Reis JC., Amarante JM., et al. Fournier's gangrene: a review of 43 reconstructive cases. *Plast Reconstr Surg*. 2007, 119(1): 175–184.
17. Black PC., Friedrich JB., Engrav LH., et al. Meshed unexpanded split-thickness skin grafting for reconstruction of penile skin loss. *J Urol*. 2004, 172(3): 976–979.
18. Hirshowitz B., Moscona R., Kaufman T., et al. One-stage reconstruction of the scrotum following Fournier's syndrome using a probable arterial flap. *Plast Reconstr Surg*. 1980, 66(4): 608–612.
19. Chen SY., Fu JP., Chen TM., et al. Reconstruction of scrotal and perineal defects in Fournier's gangrene. *J Plast Reconstr Aesthet Surg*. 2011, 64(4): 528–534.
20. Hallock G. Scrotal reconstruction following fournier's gangrene using the medial thigh fasciocutaneous flap. *Annals of Plastic Surgery*. 1990, 24(1): 86–90.
21. Spyropoulou GA., Jeng SF., Demiri E., et al. Reconstruction of perineoscrotal and vaginal defects with pedicled anterolateral thigh flap. *Urology*. 2013, 82(2): 461–465.
22. Kuzaka B., Wróblewska MM., Borkowski T., et al. Fournier's gangrene: clinical presentation of 13 cases. *Med Sci Monit*. 2018, 24: 548–555.
23. Toia F., D'Arpa S., Massenti MF., et al. Perioperative antibiotic prophylaxis: a prospective study of 1100 adult patients. *J Plast Reconst Aesthet Surg*. 2012, 65(5): 601–609.
24. Insua-Pereira I., Costa FP., Teixeira S., et al. Fournier's gangrene: a review of reconstructive options. Cent *European J Urol*. 2020, 73(1): 74–79.

Massimiliano Tripoli PhD
Plastic and Reconstructive Surgery,
Department of Surgical, Oncological and
Oral Sciences University of Palermo
Via del Vespro 129
90127 Palermo
Italy
e-mail: matripoli@yahoo.it

Submitted: 17.12.2020
Accepted: 10.5.2021

doi: 10.48095/ccachp2021102

Reconstructive and esthetic breast surgery after solid organ transplantation – a systematic review, proposal of a novel protocol and case presentations

R. B. Basso, M. E. Salto, H. F. Mayer

Plastic Surgery Department, University of Buenos Aires School of Medicine, Hospital Italiano de Buenos Aires University Institute, Buenos Aires, Argentina

Summary

Introduction: Great advancements in solid organ transplantation (SOT) have allowed patients to have better chances to survive longer and enjoy a quality life after surgery. This increasing number of SOTs and improved long-term survival rates lead to an increasing demand for plastic, esthetic and reconstructive breast procedures. **Material and methods:** A literature search following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and using searching terms related to esthetic and reconstructive breast surgery was conducted across three databases: PubMed, Scopus and Google Scholar. Included articles were analyzed to extract data points of interest including patient age, type of surgery, organ transplanted, underlying conditions associated with organ transplantation, follow-up, immunosuppressive drugs and their side effects, perioperative management and complications related to the breast plastic procedures in SOT recipients. **Results:** A total of 1,298 articles were retrieved from the mentioned electronic databases. Eight full articles were finally included in this systematic review. In these articles, a total of 41 cases of breast plastic surgery after solid organ transplantation were reported. Procedures were esthetic in nature in 26.83% of cases (11 of 41 cases) and reconstructive in 73.17% of them (30 of 41 cases). No deaths were reported. **Conclusions:** Although esthetic and reconstructive breast surgery could be performed safely in SOT recipients, the dosage of immunosuppression and patient's overall health status with regard to the length and extent of the planned procedure should always be taken into account. From the literature data analysis, it is not possible to draw a statistical conclusion that the complication rate of surgery in immunosuppressed post-transplant patients is the same as in normal, not immunosuppressed population. Further and more valid clinical studies are warranted.

Key words

plastic surgery – breast augmentation – breast reduction – breast reconstruction – solid organ transplantation – transplant patient – immunosuppressive therapy.

Basso RB.,Salto ME., Mayer HF. Reconstructive and esthetic breast surgery after solid organ transplantation – a systematic review, proposal of a novel protocol and case presentations. Acta Chir Plast. 2021, 63(3): 102–112.

Introduction

Great advancements in solid organ transplantation (SOT) have allowed patients to have better chances to survive longer and enjoy a quality life after surgery. The number of organ transplant recipients all around the world has risen annually, with a 7.25% overall increase between 2015 and 2017 [1]. This increasing number of SOTs and improved long-term survival rates lead to an increasing demand for plastic, esthetic and reconstructive procedures. Furthermore, improved surgical techniques and the development of immunosuppressive agents have also fueled this trend [2,3]. Nevertheless, the use of immunosuppressive agents in patients undergoing esthetic and reconstructive surgeries might result in more complications if compared to patients who are not treated with these drugs [4]. These problems require special attention and should not be underestimated.

Studies on reconstructive and esthetic plastic breast surgery in SOT recipients seems scanty. In this study, a systematic literature review with summarized outcomes from the available studies is presented. On the other hand, there is no protocol to define specific precautions when performing general esthetic and reconstructive surgery on transplant organ recipients. Therefore, we summarized special considerations regarding immunosuppressive therapy as well as perioperative management when performing breast procedures presenting a novel protocol. Representative cases of breast plastic surgery in transplant recipients are also presented.

Material and methods

In January 2020, a literature search was conducted across three databases using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). PubMed, Scopus, Google Scholar were systematically used searching the following terms: "allotransplantation", "solid organ transplant", "organ transplantation", "transplant recipient", "plastic surgery", "reconstructive surgical procedures", "breast cancer", "mastectomy", "breast surgery", "breast reduction", "breast augmentation", "breast reconstruction", "mammoplasty" and "mastopexy".

The inclusion criteria were limited to articles with clinical data of esthetic and reconstructive breast surgery in SOT patients with detailed description of reported cases. Articles that were not written in English were excluded. Two researchers carefully scrutinized to determine which of these articles were relevant to the study and evaluated with respect to the inclusion criteria, and any disagreements were resolved through consensus with a third reviewer. References from included articles were also examined for additional studies of interest. Fig. 1 illustrates the complete search process that followed the PRISMA guidelines [5].

Included articles were then analyzed to extract data points of interest including patient age, type of surgery, organ transplanted, underlying conditions associated with organ transplantation, follow-up, immunosuppressive drugs and their side effects, perioperative management and complications related to the breast plastic procedures in SOT recipients.

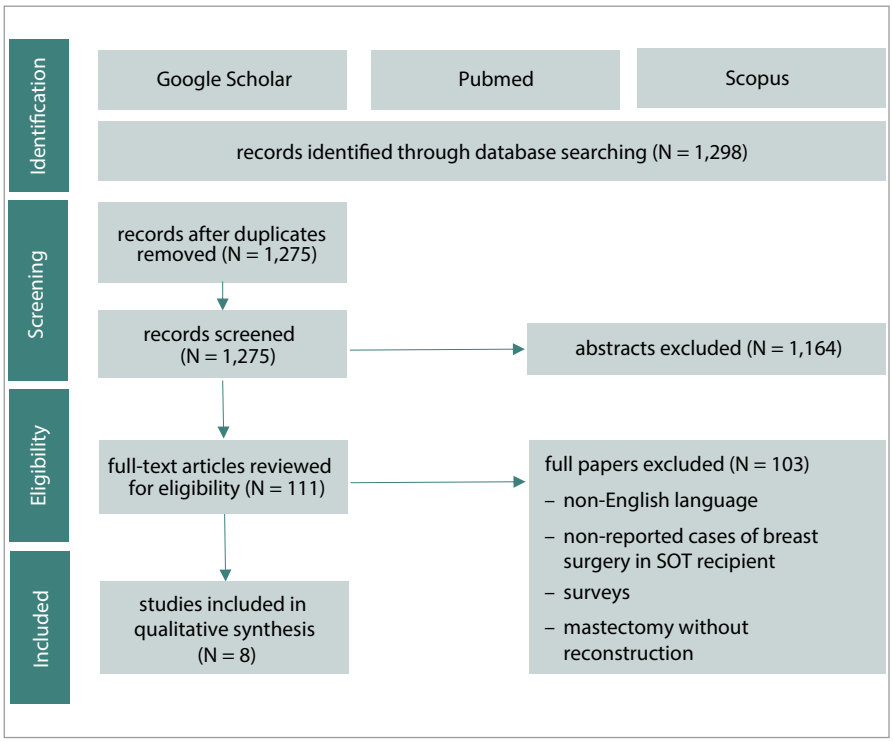


Fig. 1. PRISMA flow diagram depicting the flow of information through the different phases of our systematic review.
PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-analyses

Results

Bibliographic search

A total of 1,298 articles were retrieved from the mentioned electronic databases. Duplicated studies and abstracts not-related to our search were removed resulting in 111 citations full-text for review. Eight full articles were finally included in this systematic review based on the described search strategy. In these articles, a total of 41 cases of breast plastic surgery after solid organ transplantation were reported. Those represented more than one surgery in cases that required a second stage reconstruction. The average patient age was 41.9 years (range 15–65 years). The time after SOT until breast surgery ranged from 16 months to 25 years (average time 7.26 years). The procedures were esthetic in nature in 26.83% of cases (11 of 41 cases) and reconstructive in 73.17% of them (30 of 41 cases). The most frequent SOT involved was kidney transplantation with 41.46%. The percentage of heart transplants, pancreas transplants, lung transplants and liver transplants were 17.07%, 9.75%, 2.43% and 7.31% respectively. Twenty-two percent of SOT involved were not described. Minor complications were detected in 13 cases (31.7%), while in two opportunities major surgical complications required returning to the operating room (4.88%). No death was reported. The results are summarized in Tab. 1.

Immunosuppressive drugs

Common adverse effects of immunosuppressants are well documented and include metabolic side effects, toxicities and infectious complications. Those are described in Tab. 2. Current standardization of immunosuppressive protocols helps to predict the susceptibility to infection and impairment of wound healing [6].

The type, dose, and long-term duration of immunosuppressive agents utilized to prevent graft rejection after transplantation have all been shown to affect the risk of cancer development without identification of an individual agent in cancer outcomes since a variety of drugs are needed during any stage for prevention of organ rejection [7]. It is possibly related to chronic inflammation and weakness of cellular immune responses.

Steroids

These drugs are known to inhibit all phases of wound healing, wound contraction, collagen deposition, epithelialization. This effect is due to their interruption of the normal inflammatory response. Glucocorticoids lower the levels of transforming growth factor-B (TGF-B) and insulin-like growth factor-1 (IGF-1) in wounds. Both growth factors are necessary in the inflammatory cascade leading to collagen synthesis. The resulting inhibitory effects affect wound healing, delay of recovered wound tensile strength and increase friability of the skin and superficial blood vessels carrying important surgical implications [8].

Steroids are associated not only with delayed wound healing and increased risk of infection but also with a large number of side effects such as hypertension, hyperglycemia, hyperlipidemia, obesity, effects on bone metabolism, weight gain, eye disorders, Cushing's syndrome depending on the timing of administration [4,6,8].

The elimination of steroids or doses < 10mg/day in the post-transplant immunosuppression regimen has greatly contributed to improved physical appearance and better wound healing in these patients. If corticosteroids are necessary during the postoperative period, they should be administered three or more days after wound healing to reduce inhibitory effects on wound healing [4].

Some patients still require chronic low-dose steroids. Receiving their usual dose of corticosteroids instead of a stress dose plays a significant role in reducing side effects related to wound breakdown, psychiatric disturbances, and blood sugar control in elective surgery [9]. If any signs of adrenal insufficiency appear as a long-term consequence of corticosteroid therapy, steroid replacement giving low peak doses every 8 h and tapering to baseline over a short period of time, such as 1–3 days is recommended to mimic the physiologic response to stress [9].

The timing of esthetic breast surgery procedures relative to the transplant procedure itself is critical. All elective surgical procedures should be postponed during any interval requiring reintroduction or increased dose of steroids. Papadopoulos et al reported a series of 41 transplant recipients undergoing plastic surgery procedures. In their series, only patients undergoing plastic surgery procedures early after transplantation experienced an increased morbidity [2]. It is advised that mean elapsed time after transplant should be more than 6 months for elective cases to prevent graft rejection trying to avoid acute rejection episodes [9].

An univariate analysis was performed by Sbitany et al to assess the correlation between the various immunosuppressive medications and the frequency of any complication in microvascular free tissue transfer. This analysis illustrates a statistically significant association between prednisone and complications we mentioned before, but no statistically significant associations of other drugs were found [9].

Cyclosporine

Cyclosporine-treated patients more often experience cosmetic side effects such as acne, hirsutism and gingival hyperplasia, whereas gastrointestinal complications and neurotoxic effects are more frequent in tacrolimus-treated patients. Gigantomastia and breast lumps have also been described in a kidney transplant recipient. Rolles and Calne were the first to describe breast lumps after receiving an allograft under cyclosporine A treatment in 1980 [10,11]. Switching from cyclosporine to tacrolimus after an early evaluation of hormones and a breast ultrasound was found to be effective not only to prevent the progression of nodules but also disappearance of lumps avoiding the need for breast surgery [12]. Cyclosporine A has no proven effect in the process of wound healing [13].

Sirolimus

Special attention for plastic surgeons is warranted in the subpopulation of transplant patients who are maintained on sirolimus. This drug, reserved for patients who do not tolerate other immunosuppressive agents, is a well-known inhibitor of fibroblast and cell proliferation. The potential effects of sirolimus on inhibition of wound healing, which are seen in some patients, are due to the drug's blockage of the response to interleukin-2 [14]. The use of sirolimus might be a relative contraindication to esthetic surgery. Its use has been related to a high rate of wound complications when compared to tacrolimus despite lowering the administered dose [15]. The transplant team should evaluate switching sirolimus to an alternate medication during the perioperative time. Awareness of the altered pathophysiology and special requirements of the immunosuppressed host will prompt the surgeon to modify the treatment plans accordingly to achieve a successful outcome with a minimal incidence of complications.

Mycophenolate mofetil (MMF)

MMF has a high rate of gastrointestinal complications and leukopenia and is commonly associated with headache and fatigue [16]. As sirolimus, the use of MMF may be a relative contraindication to esthetic surgical procedures. In a retrospective study, MMF was found to cause more wound infection and non-infectious wound complications when compared to azathioprine in kidney recipients [17].

Azathioprine

Azathioprine is a purine analogue prodrug that requires enzyme action to convert into active compounds. As cyclosporine, azathioprine has no proven effect in the process of wound healing [2]. Other side effects related to this drug are leukopenia, gastrointestinal disturbances or elevated liver function

Tab. 1. Characteristics of studies comparing breast procedures outcomes for solid organ transplantation.

Patient	First author year	Age years	Surgery	Reason for mastectomy	Reason for transplant	Years after transplant	Solid organ	Medication	Complication	Treatment
1	Cervelli [11] 1999	41	breast reduction	gigantomastia and breast lumps	end-stage renal disease	7	kidney	CsA	N/A	N/A
2	Lee [31] 2008	N/A	free TRAM	N/A	N/A	N/A	kidney	CsA/pred	intraoperative arterial thrombosis	N/A
3	Lee [31] 2008	N/A	free TRAM	N/A	N/A	N/A	kidney	CsA/pred	N/A	N/A
4	Lee [31] 2008	N/A	DIEP	N/A	N/A	N/A	heart	Tac	N/A	N/A
5	Shi [37] 2014	15	bilateral reduction mammoplasty	N/A	N/A	1 year 5 months	heart	pred/CsA/MMF	N/A	N/A
6	Koonce [23] 2015	N/A	bilateral tissue expander	invasive lobular carcinoma	familial idiopathic pulmonary fibrosis	1 year 5 months	lung	N/A	cellulitis	antibiotics
7	Koonce [23] 2015	N/A	bilateral tissue expander with alloderm	invasive ductal carcinoma	dilated cardiomyopathy from adriamycin	N/A	heart	N/A	N/A	N/A
8	Koonce [23] 2015	N/A	bilateral LDMF	invasive ductal carcinoma	congestive cardiomyopathy	N/A	heart	N/A	N/A	N/A
9	Koonce [23] 2015	N/A	bilateral LDMF with tissue expander	family history/increased risk	radiation for Hodgkin lymphoma	N/A	heart	N/A	delayed healing of mastectomy flap	second intention wound healing
10	Koonce [23] 2015	N/A	bilateral permanent implant with strattice and alloderm	invasive ductal carcinoma	cardiomyopathy from tocolytic drug	25	heart	N/A	N/A	N/A
11	Koonce [23] 2015	N/A	LDMF with tissue expander	invasive ductal carcinoma	Budd Chiari	4	liver	N/A	mastectomy skin flap necrosis	N/A
12	Koonce [23] 2015	N/A	immediate permanent implant	ductal carcinoma in situ	primary biliary cirrhosis	N/A	liver	N/A	no	N/A
13	Koonce [23] 2015	46	bilateral tissue expander with alloderm	invasive ductal carcinoma	insulin-dependent diabetes mellitus	4	pancreas	N/A	grade III/IV capsular contracture	N/A
14	Koonce [23] 2015	N/A	bilateral tissue expander	family history/increased risk	end-stage renal disease	N/A	kidney/pancreas	N/A	N/A	N/A
15	Koonce [23] 2015	N/A	LDMF with tissue expander	invasive ductal carcinoma	end-stage renal disease	10	kidney/pancreas	N/A	N/A	N/A
16	Koonce [23] 2015	N/A	bilateral tissue expander	invasive ductal carcinoma	end-stage renal disease	N/A	kidney	N/A	infected expander	N/A
17	Koonce [23] 2015	N/A	bilateral tissue expander	invasive ductal carcinoma	end-stage renal disease	N/A	kidney	N/A	N/A	N/A
18	Koonce [23] 2015	N/A	bilateral tissue expander	invasive lobular carcinoma	polycystic kidney disease	N/A	kidney	N/A	N/A	N/A
19	Koonce [23] 2015	N/A	left tissue expander/right tissue expander with alloderm	invasive ductal carcinoma/ductal carcinoma in situ	focal segmental glomerulosclerosis	N/A	kidney	N/A	N/A	N/A

20	Koonce [23] 2015	N/A	bilateral tissue expander with alloderm	invasive ductal carcinoma	tubular interstitial disease	18	kidney	N/A	left partial nipple necrosis	N/A
21	Koonce [23] 2015	N/A	bilateral tissue expander with alloderm	ductal carcinoma in situ	chronic glomerulonephritis	N/A	kidney	N/A	cellulitis	N/A
22	Koonce [23] 2015	N/A	free TRAM	ductal carcinoma in situ	reflux nephropathy	N/A	kidney	N/A	abdominal seroma	N/A
23	Zellner [40] 2016	46	bilateral TRAM after bilateral mastectomy	N/A	nonischemic cardiomyopathy	N/A	heart	CsA/MMF	fat necrosis/ventral hernia	TRAM revision / VHR
24	Zellner [40] 2016	53		N/A	diabetes mellitus	N/A	kidney × 2	MMF/tac/pred	postoper. hypoxia	hospitalized × 2 days
25	Zellner [40] 2016	50	tissue expander placement after mastectomy	N/A	diabetes mellitus	N/A	kidney and pancreas	CsA/pred/MMF	bilateral hematomas	hematoma evacuation
26	Zellner [40] 2016	N/A	minor revision of breast reconstruction	N/A	N/A	N/A	N/A	N/A	N/A	N/A
27	Zellner [40] 2016	N/A	minor revision of breast reconstruction	N/A	N/A	N/A	N/A	N/A	N/A	N/A
28	Zellner [40] 2016	N/A	minor revision of breast reconstruction	N/A	N/A	N/A	N/A	N/A	N/A	N/A
29	Zellner [40] 2016	N/A	free flap reconstruction	N/A	N/A	N/A	N/A	N/A	N/A	N/A
30	Zellner [40] 2016	N/A	breast reconstruction	N/A	N/A	N/A	N/A	N/A	N/A	N/A
31	Zellner [40] 2016	N/A	implant reconstruction	N/A	N/A	N/A	N/A	N/A	N/A	N/A
32	Zellner [40] 2016	N/A	reduction mammaplasty	N/A	N/A	N/A	N/A	N/A	N/A	N/A
33	Zellner [40] 2016	N/A	reduction mammaplasty	N/A	N/A	N/A	N/A	N/A	N/A	N/A
34	Zellner [40] 2016	N/A	reduction mammaplasty	N/A	N/A	N/A	N/A	N/A	N/A	N/A
35	Zellner [40] 2016	N/A	reduction mammaplasty	N/A	N/A	N/A	N/A	N/A	N/A	N/A
36	Zellner [40] 2016	N/A	reduction mammaplasty	N/A	N/A	N/A	N/A	N/A	N/A	N/A
37	Basic-Jukic [29] 2018	36	breast augmentation	N/A	N/A	4 years	kidney	basiliximab/tac/MMF/pred	renal allograft rejection 6 months later	conservative treatment
38	Basic-Jukic [29] 2018	52	breast reconstruction after mastectomy	N/A	N/A	N/A	kidney	basiliximab/CsA/MMF/pred	renal allograft rejection	conservative treatment
39	Ozkan [39] 2018	48	reduction mammaplasty	N/A	N/A	2 years	liver	pred/tac/MMF	N/A	N/A
40	Ozkan [39] 2018	46	reduction mammaplasty	N/A	N/A	N/A	kidney	pred/tac/MMF	N/A	N/A
41	Pan [40] 1997	28	reduction mammaplasty	gigantomastia and breast lumps	end-stage renal disease	3 years	kidney	pred/CsA/aza	no	N/A

aza – azathioprine, CsA – cyclosporine A, DIEP – deep inferior epigastric perforators, LDMF – latissimus dorsi myocutaneous flap, mepred – meprednisone, MMF – mycofenolate, N/A – not available, pred – prednisone, tac – tacrolimus, TRAM – transverse rectus myocutaneous, VHR – ventral hernia repair

Tab. 2. Side effects of drugs in chronic immunosuppression.

Drug	Mechanism of action	Side effects concerning plastic surgeons	Metabolic effects	Digestive effects	Hematologic side effects	Skin side effects	Toxicity	Other
steroids	inhibition of IL-1 and IL-6 synthesis; blocking the proliferation of T cells	delayed wound healing/wound infection/ non-infectious wound complications	hypertension/ hyperglycemia/ hyperlipidemia/ obesity/ Cushing's syndrome/ osteoporosis	nausea/ abdominal pain	leukocytosis/ lymphopenia	acne/ hirsutism	neurotoxicity	blurred vision/ insomnia
MMF	antiproliferative activity towards T and B cell population; inhibition of purine synthesis	delayed wound healing/wound infection/ non-infectious wound complications	anorexia/ hyperkalemia/ hyperglycemia	nausea/ vomiting/ diarrhea/ abdominal pain	leukopenia/ anemia/ thrombocytopenia/ pancytopenia	flushed/dry skin	neurotoxicity	joint pain
cyclosporine	calcineurin inhibitor; inhibition of T cell activation by blocking IL-2 synthesis and release	non-infectious wound complications/breast lumps	hyperglycemia/ hyperuricemia/ hyper-cholesterolemia/ hyperkalemia/ hypertension	nausea/ vomiting/ diarrhea/ abdominal pain	bleeding (gums/urine/ vomit)	acne/ hirsutism/ skin rashes	nefrotoxicity/ neurotoxicity/ hepatotoxicity	gingival hyperplasia
tacrolimus	calcineurin inhibitor; inhibition of T cell dependent calcium activation and proliferation	N/A	hyperglycemia	nausea/ vomiting/ abdominal pain	anemia/ neutropenia	hypersensivity /acne/ Itching/ redness	nefrotoxicity/ neurotoxicity	headache/ muscle pain
syrolimus	mTOR inhibitor	delayed wound healing	hypocalcaemia/ hyper-triglyceridaemia/ hyper-cholesterolemia/ increased LDH	nausea/ vomiting/ diarrhea/ abdominal pain	leukopenia/ anemia/ thrombocytopenia	acne	nefrotoxicity	joint pain/ osteonecrosis/ TVP
azathioprine	analog of purines; inhibition of T cell proliferation	wound infection/ non-infectious wound complications/ breast lumps	anorexia	nausea/ vomiting/ diarrhea/ pancreatitis/ cholecystiti/ diverticulitis	leukopenia/ anemia/ thrombocytopenia/ pancytopenia	alopecia/ skin rashes	hepatotoxicity	joint pain/ pneumonitis
basiliximab	monoclonal antibody; IL-2 antireceptor	N/A	hypertension	nausea/ vomiting/ diarrhea/ constipation/ abdominal pain	leukopenia	acne	neurotoxicity	joint pain/ hypersensitivity reactions

IL-2 – interleukin 2, mTOR – serin-threonine kinase, LDH – lactate dehydrogenase, MMF – mycophenolate mofetil, N/A – not available, TVP – transplant vasculopathy

Tab. 3. Proposed management protocol for breast plastic surgery in solid organ transplantation patients.

Preadmission	Work together with transplant surgeon, organ-specific specialist and mastologist
	Careful patient selection
	Avoid combined surgical procedures
	Perform procedures 6 or more months after SOT
	Thorough preoperative evaluation of SOT patient
	Knowledge of immunosuppressive drugs, side effects and interactions
	Sirolimus or MMF might be a relative contraindication
	Suspension of steroids or doses < 10 mg/day
	Avoid surgery requiring reintroduction or increased dose of steroids
	Reduce immunosuppression dosage to the lowest possible
Preoperative	Antibiotic, stress ulcer and VTE prophylaxis administration as general population
	Antibiotics prophylaxis should be administered 60–120 min. before incision
	Special consideration regarding each solid organ transplant care
	Anesthetics considerations on case-by-case basis
Intraoperative	Bupivacaine and ropivacaine are safe if used as local anesthetics
	Operative time shorter for a lower surgical stress level
	Use of ADM might be a relative contraindication
	No contraindication of using silicone breast implant
	Closing wound without tension
Postoperative	Early mobilization
	NSAIDs should be avoided in postoperative pain management
	Delay steroid administration by 3 or more days (whenever possible)
	Leave external sutures for at least 3 weeks

ADM – acellular dermal matrix, MMF – mycophenolate mofetil, NSAIDs – non-steroidal anti-inflammatory drugs, SOT – solid organ transplantation, VTE – venous thromboembolism

tests. The side effects of most common drugs used in immunosuppressive therapy for SOT recipients that the plastic surgeon must know are summarized in Tab. 3.

Management considerations

Anesthesiology

There is no ideal anesthetic for the use in organ transplant recipients. When performing a non-transplant surgery, perioperative anesthetic management in the majority of recipients is like the standard practice for any patient. Despite that, specific considerations should be kept in mind such as the adverse effects of immunosuppressive drugs, its interaction with anesthetic drugs, the potential of organ rejection, blood product administration, as well as the risk and benefits of invasive monitoring in these patients [9,18]. The indications for invasive monitoring will be based on other criteria than the presence of immunosuppression and the condition after organ transplantation. Another issue is the importance of keeping the operative time shorter for a lower surgical stress level [18,19]. Minimal invasiveness and reduced operative time will be essential for these patients.

Special care must be taken into consideration regarding each SOT case, such as avoiding non-steroid anti-inflammatory drugs in kidney transplants recipients [18]. We suggest working with an experienced anesthetist who knows pharmacokinetic and pharmacodynamic interactions among the drugs that the patients take after transplantation. All of our patients are managed by anesthesiologists with long experience in working with this kind of patient. Also, we recommend avoiding long or combined surgical procedures and guiding patients in the direction of separating the sessions or correcting the most desired disorder.

Antibiotic prophylaxis

Transplant recipients have an increased susceptibility to infection, but the degree of risk is not uniform throughout the post-transplant period. The risk of infection is higher during the periods of greatest immunosuppression. This is usually during the first 6 months after transplantation and during acute rejection episodes. At present, there is no evidence that prolonged antibiotic prophylaxis protocols provide advantages to preventing infectious complications in some groups of patients, and could predispose to infections [20]. A systematic review compared the use of extended antibiotics versus single dose prophylaxis prior breast surgery with implants and demonstrated a significantly reduced incidence of surgical site infection with extended prophylactic antibiotics (4.6 vs. 11% average infection rate) especially at "higher risk" group of immunosuppressed patients [21]. Since there is no data suggesting a different bacteriology of surgical site infections in these patients, antimicrobial cover-

age need not to be expanded to include atypical or opportunistic organisms [22]. We recommend the same antibiotic prophylaxis we use with the general population.

Wound healing

The risk of wound-healing complications is higher in transplant patients maintained on steroids chronically. In 2015, Koonce et al demonstrated non-delayed wound healing on patients continuing with immunosuppression drugs (tacrolimus, azathioprine, prednisone, cyclosporine, or MMF) despite none of them were using sirolimus [23]. Surgical wound dehiscence had a negative impact on the physical and social functioning, and bodily pain dimensions of health-related quality of life and on mental health [24]. The impaired wound healing and delay in the attainment of expected wound tensile strength in patients receiving corticosteroids have important surgical implications. Closing the wound without tension is crucial in transplant patients. It is important to use suture materials that have prolonged survival time and to leave sutures, tapes, or clips in the skin closure for at least 3 weeks since the tensile strength of the most absorbable suture materials weakens in the time required to obtain adequate strength in the wound [25]. Since immunosuppressive agents are used in combinations, their individual potential for wound complications is difficult to estimate.

Representative cases

Case 1. A 47-year-old female who underwent a liver transplantation, suffered transplant rejection requiring re-transplantation 30 years ago due to glycogenosis type 1 disease at our hospital. She was interested in breast augmentation and was referred to us by the medical transplant team. Her immunosuppressive therapy included tacrolimus, mycophenolate mofetil, azathioprine, meprednisone (from 20 mg/day to 2 mg/day). In addition, she was receiving levothyroxine for hypothyroidism and acenocoumarol due to hepatic thrombosis. The preoperative evaluation of liver function was close to normal. The immunosuppressive drugs were routinely monitored and there was a switch from anticoagulant to enoxaparin sodium injection. She received a preoperative stress dose steroid (hydrocortisone hemisuccinate 50 mg i.v. prior to the procedure), and prophylactic antibiotic (cefazolin). The patient's perioperative course was uneventful. After a 4-year-follow-up, she had not reported any abnormality or complications (Fig. 2).

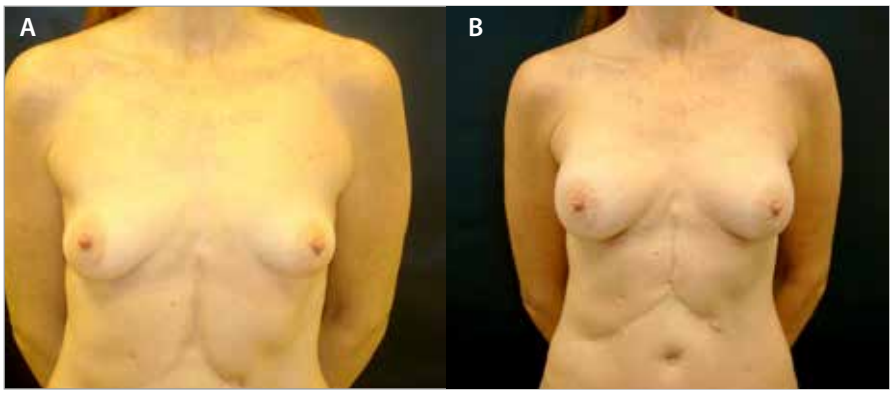


Fig. 2. A 47-year-old female who underwent a liver transplantation was interested in breast augmentation and was referred to us by the medical transplant team; A) preoperative anterior view; B) postoperative anterior view at one year.

Case 2. A 59-year old female patient, a liver transplant recipient 5 years earlier due to autoimmune hepatitis with the presence of antinuclear antibodies (ANA), was referred to us by a breast surgeon after performing a right radical modified mastectomy. No other comorbidity was found. Her immunosuppressive therapy included tacrolimus, MMF, meprednisone (from 20 mg/day to 2 mg/day). She received chemotherapy (cyclophosphamide and doxorubicin), radiotherapy treatment and the same immunosuppressive drugs as she had used before. Her liver function tests were close to normal. A two-stage implant-based breast reconstruction was carried out placing first a 450 cm^3 breast tissue expander into a subpectoral pocket.

In order to avoid a painful delayed expansion process and only after considering the associated risks, we decided to start expansions as soon as wound healing was completed and the surgical scar looked strong and solid. At week 3, we started injecting 60 cm^3 per week, completing the process 6 weeks later. A second stage replacing the expander by the permanent breast implant and a simultaneous contralateral symmetrization with a silicone breast implant was carried out 5 months later. As the patient was previously irradiated, she received a week of antibiotic prophylaxis with trimethoprim sulfamethoxazole [26]. She recovered without any complication (Fig. 3). As we recommend avoiding long surgical procedures, the possibility of long autologous breast reconstruction was not considered.

Case 3. A 32-year old male patient who underwent a kidney transplant 5 years earlier due to end-stage renal disease and at that time suffering from bilateral gynecomastia was referred to us by his nephrologist. No other comorbidity was found. His immunosuppressive therapy included a triple scheme including cyclosporine, steroids and aziatropina. He underwent a bilateral subcutaneous mastectomy the postoperative recovery of which was uneventful. During follow-up, hypertrophic scarring was detected in both sides requiring scar revision

Fig. 3. A 59-year old female patient, a liver transplant recipient 5 years earlier was referred to us by a breast surgeon after performing right radical modified mastectomy for breast reconstruction; A) preoperative anterior view; B) postoperative view at 3 months after placing an expander; C) late postoperative view at 1 year after replacing an expander by the permanent implant and symmetrization with a breast implant.

under local anesthesia without any complications (Fig. 4).

In all of these patients, preoperative evaluation was carried in strict collaboration with the transplant surgery departments. All of our patients received the usual antibiotics for those procedures despite being transplant recipients. In all of our patients we used permanent sutures in the different layers of closure. External sutures were avoided, and when required they were removed after one month. They were a true challenge for the entire medical team, where multidisciplinary work enabled a successful end to the all three patients. A proposed protocol of management is presented in Tab. 2.

Discussion

As time goes by, transplant recipient patients have greatly benefited from improved outcomes and a reduced rate of complications due to substantial advances within the last decade [3]. The improved long-term survival rates in transplant recipient patients has led to an increased demand for plastic and reconstructive procedures [2,3].

There is no protocol to define specific precautions when performing general esthetic and reconstructive surgery on transplant organ recipients. These considerations are usually independent of the type of transplant immunosuppressed state. When transplant recipients require non-transplant surgery, immune competence can be altered from the stress of surgery, acute illness, or disruption of the regimen by inexperienced providers. A coordinated teamwork between the plastic surgery and the transplant surgery teams is very important, since a successful and gratifying outcome is possible when all the available resources are brought to bear in the care of these complex patients expecting a comparable degree of success following plastic surgery as the remaining segment of the population [9].

Just case reports, case series or survey-based studies were found in this systematic review, which denotes the need for studies with less bias and greater validity. Indeed, plastic surgeons need to design stronger studies at higher levels of evidence to reach valid conclusions on any topic. Nevertheless, case series and case reports will still be needed for rare conditions and new technical developments among other reasons [27]. Another limitation present in this systematic review is the strong heterogeneity between the studies, which did not make it possible to carry out a quantitative analysis by a meta-analysis and to compare the results.

As expected, reconstructive breast procedures in SOT patients were much more frequent than esthetic ones with the 3/1 ratio (reconstructive/esthetic). In 2016, 1,308 plastic surgeons from all the world participated in a web-based survey related to esthetics surgery in SOT patients. Interestingly, 30% of them per-

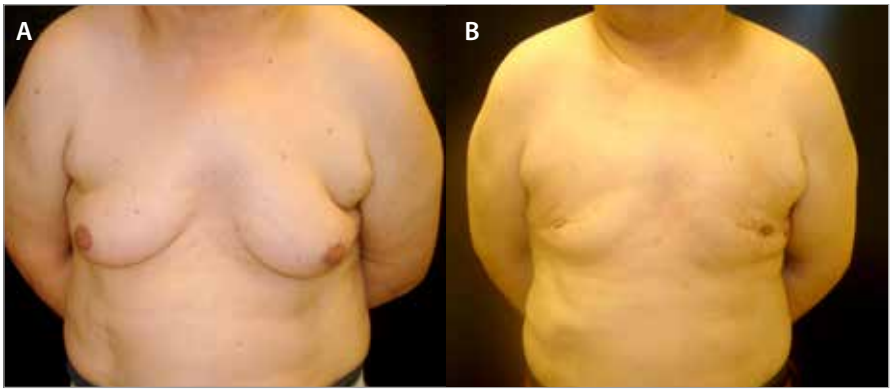


Fig. 4. A 32-year old male patient who underwent a kidney transplant and was suffering from bilateral gynecomastia was referred to us by his nephrologist; A) a preoperative anterior view; B) postoperative view at 14 months.

formed esthetic procedure on SOT recipients where 92% of respondents reported no complications [19]. This conclusion does not correlate with the percentage of complications reported by the patient population in this study (31.7% complications). This is one piece of evidence that valid data is not available to be statistically analyzed.

Breast augmentation is one of the most popular esthetic surgeries in many countries including ours [28,29]. Therefore, no wonder one of our representative cases was breast augmentation. Although the incidence of breast cancer in SOT recipients is comparable to that in the general population, the prognosis is generally poor [30]. Cyclosporine-treated patients often experience cosmetic side effects such as gynecomastia which was present in our male kidney transplant patient herein reported [10,11].

The use of silicone breast implants for esthetic or reconstructive purposes is controversial. Basic-Jukic et al suggested an association between silicone gel and induction of the immunological response involved in acute allograft rejection shortly after breast implant surgery based on two cases [31]. However further studies with stronger evidence are needed. On the other hand, according to recent statistics from the American Society of Plastic Surgeons, over 85% of all breast reconstructions carried out in the US and other countries are implant-based [28,32]. Both female patients, herein presented, underwent their esthetic and reconstructive procedures with silicone breast implants not presenting implant-related complications after 4 years of follow-up.

Reconstructive options after mastectomy may vary depending on the incisions required to perform transplant surgery; for example, lung transplantation that requires section of the latissimus dorsi muscle or kidney transplantation with abdominal incision and its difficulty in using the transverse rectus myocutaneous (TRAM) or deep inferior epigastric perforator (DIEP) flaps. The convenience of undergoing long reconstructive microsurgical procedures should be also carefully taken into account. Notwithstanding, Lee et al demonstrated in a multicenter retrospective study that it is safe to perform microsurgical procedures in selected transplant patients [33].

It is supposed that acellular dermal matrices (ADM), very frequently used in implant-based breast reconstruction, should not be recognized as foreign body inducing minimal or no host immune inflammatory response [34]. However, the use of ADM has been reported as a relative contraindication being immunosuppressed [35]. On the other hand, ADM-assisted breast reconstructions are usually linked to a higher likelihood of infection rate if compared to breast reconstructions without the use of ADM [36,37]. Notwithstanding, Koonce et al reported a case using ADM in bilateral breast reconstruction after kidney transplantation without any complications [23]. We suggest not to use it until further studies with stronger levels of evidence are available.

The plastic surgeon has an advantage to manage cases, especially those of esthetic nature, through careful patient selection, investigation of medications, preoperative anesthesiology consultations, and patient information for possible complications. Since esthetic plastic surgery is elective, there are many opportunities to choose the most favorable timing to perform these procedures [38]. It is critical to ensure that the patient is far enough in the postoperative course and is on a stable immunosuppressive schedule to determine the appropriate timing for elective surgery. It is advised that mean elapsed time after transplant should be more than 6 months for elective cases to prevent graft rejection trying to avoid acute rejection episodes [9]. Also, all elective surgeries should be postponed during any interval requiring reintroduction or increased dose of steroids. Unfortunately, some cases such as breast reconstruction following breast cancer are not elective, and in these cases the optimization of medication and care are of paramount importance.

Conclusions

This study represents the first systematic literature review of esthetic and reconstructive breast procedures after SOT. Only case reports, case series or survey-based studies were found in this review. However, data analysis revealed several interesting trends that may aid plastic surgeons in managing transplant recipient patients.

Although esthetic and reconstructive breast surgery could be performed safely in SOT recipients, the dosage of immunosuppression and patient's overall health status with regard to the length and extent of the planned procedure should always be taken into account. Mean elapsed time after transplant should always be more than 6 months for elective cases to prevent graft rejection trying to avoid acute rejection episodes. From the literature data analysis, it is not possible to draw a statistical conclusion that the complication rate of surgery in immunosuppressed post-transplant patients is the same as in normal, not immunosuppressed population. Further and more valid clinical studies are warranted.

Role of authors: R. B. Basso and M. E. Salto conducted the literature search, designed the flowchart and analyzed the collected data. R. B. Basso wrote the manuscript with the input from all authors. H. F. Mayer conceived the study and revised it critically for important intellectual content. All the authors approved the version to be published.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This is a review study with case reports. Our Research Ethics Committee has confirmed that no ethical approval is required.

Conflict of interest: The authors declare that they have no conflict of interest.

Patient consent: Patients signed informed consent regarding publishing their data and photographs.

References

1. Carmona M. 2017 Global Report. [online]. Available from: www.transplant-observatory.org/download/2017-activity-data-report/.

2. Papadopoulos O., Konofaos P., Chrisostomidis C., et al. Reconstructive surgery for kidney transplant recipients. *Transplant Proc.* 2005, 37(10): 4218–4222.

3. Sweis I., Tzvetanov I., Benedetti E. The new face of transplant surgery: a survey on cosmetic surgery in transplant recipients. *Aesthetic Plast Surg.* 2009, 33(6): 819–826.

4. Wang AS., Armstrong EJ., Armstrong AW. Corticosteroids and wound healing: clinical considerations in the perioperative period. *Am J Surg.* 2013, 206(3): 410–417.

5. Liberati A., Altman DG., Tetzlaff J., et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med.* 2009, 151(4): W65–W94.

6. Whitaker IS., Duggan EM., Alloway RR., et al. Composite tissue allotransplantation: a review of relevant immunological issues for plastic surgeons. *J Plast Reconstr Aesthet Surg.* 2008, 61(5): 481–492.

7. Dantal J., Soulillou JP. Immunosuppressive drugs and the risk of cancer after organ transplantation. *N Engl J Med.* 2005, 352(13): 1371–1373.

8. Sbitany H., Xu X., Hansen SL., et al. The effects of immunosuppressive medications on outcomes in microvascular free tissue transfer. *Plast Reconstr Surg.* 2014, 133(4): 552–558.

9. Gohh RY., Warren G. The preoperative evaluation of the transplanted patient for non-transplant surgery. *Surg Clin North Am.* 2006, 86(5): 1147–1166.

10. Rolles K., Calne RY. Two cases of benign lumps after treatment with cyclosporin A. *Lancet.* 1980, 2(8198): 795.

11. Cervelli V., Orlando G., Giudiceandrea F., et al. Gigantomastia and breast lumps in a kidney transplant recipient. *Transplantation Proc.* 1999, 31(8): 3224–3225.

12. Iaria G., Pisani F., De Luca L., et al. Prospective study of switch from cyclosporine to tacrolimus for fibroadenomas of the breast in kidney transplantation. *Transplantation Proc.* 2010, 42(4): 1169–1170.

13. Bootun R. Effects of Immunosuppressive therapy on wound healing. *Int Wound J.* 2013, 10(1): 98–104.

14. Sehgal SN. Rapamune (RAPA, rapamycin, sirolimus): mechanism of action immunosuppressive effect results from blockade of signal transduction and inhibition of cell cycle progression. *Clin Biochem.* 1998, 31(5): 335–340.

15. Dean PG., Lund WJ., Larson TS., et al. Wound-healing complications after kidney transplantation: a prospective, randomized comparison of sirolimus and tacrolimus. *Transplantation.* 2004, 77(10): 1555–1561.

16. Petrò L., Ponti A., Roselli E., et al. Perioperative management for patients with a solid organ transplant. *Practical Trends in Anesthesia and Intensive Care.* 2018, Springer, Cham.

17. Humar A., Ramcharan T., Denny R., et al. Are wound complications after a kidney transplant more common with modern immunosuppression? *Transplantation.* 2001, 72(12): 1920–1923.

18. Herborn J., Parulkar S. anesthetic considerations in transplant recipients for nontransplant surgery. *Anesthesiol Clin.* 2017, 35(3): 539–553.

19. Vandegrift MT., Nahai F. Is aesthetics surgery safe in the solid organ transplant patient? An international survey and review. *Aesth Surg J.* 2016, 36(8): 954–958.

20. Berry PS., Rosenberger LH., Guidry CA., et al. Intraoperative versus extended antibiotic prophylaxis in liver transplant surgery: a randomized controlled pilot trial. *Liver Transpl.* 2019, 25(7): 1043–1053.

21. Huang N., Liu M., Yu P., et al. Antibiotic prophylaxis in prosthesis-based mammoplasty: a systematic review. Int J Surg. 2015, 15: 31–37.
22. Bliven K., Snow K., Carlson A., et al. Evaluating a change in surgical antibiotic prophylaxis in kidney transplant recipients. *Cureus.* 2018, 10(10): e3433.

23. Koonce SL., Giles B., McLaughlin SA., et al. Breast reconstruction after solid organ transplant. *Ann Plast Surg.* 2015, 75(3): 343–347.

24. Corrêa NFM., de Brito MJ., de Carvalho Resende MM., et al. Impact of surgical wound dehiscence on health-related quality of life and mental health. *J Wound Care.* 2016, 25(10): 561–570.

25. Cohen M., Pollak R., Garcia J., et al. Reconstructive surgery for immunosuppressed organ-transplant recipients. *Plast Reconstr Surg.* 1989, 83(2): 291–295.

26. Mirzabeigi MN., Lee M., Smartt JM., et al. Extended trimethoprim/sulfamethoxazole prophylaxis for implant reconstruction in the previously irradiated chest wall. *Plast Reconstr Surg.* 2012, 129(1): 37–45.

27. Agha RA., Devesa M., Whitehurst K., et al. Levels of evidence in plastic surgery – bibliometric trends and comparison with five other surgical specialties. *Eur J Plast Surg.* 2016, 39(5): 365–370.

28. American Society of Plastic Surgeons 2019 statistics. [online]. Available from: https://www.plasticsurgery.org/documents/News/Statistics/2019/plastic-s urgery-statistics-full-report-2019.pdf.

29. Mayer HF., Loustau HD.. Immediate prosthetic breast reconstruction in the previously augmented patient. *J Plast Reconstr Aesthet Surg.* 2015, 68(9): 1311–1313.

30. Wong G., Au E., Badve SV., et al. Breast Cancer and Transplantation. *Am J Transplant.* 2017, 17(9): 2243–2253.

31. Basic-Jukic N., Ratkovic M., Radunovic D., et al. Association of silicone breast implants and acute renal allograft rejection. *Med Hypotheses.* 2019, 123: 81–82.

32. Mayer HF., de Belaustegui EA., Loustau HD. Current status and trends of breast reconstruction in Argentina. *J Plast Reconstr Aesthet Surg.* 2018, 71(4): 607–609.

33. Lee AB., Dupin CL., Colen L., et al. Microvascular free tissue transfer in organ transplantation patients: Is it safe? *Plast Reconstr Surg.* 2008, 121(6): 1986–1992.

34. Macadam SA., Lennox PA. Acellular dermal matrices: use in reconstructive and aesthetic breast surgery. *Can J Plast Surg.* 2012, 20(2): 75–89.

35. Rebowe RE., Allred LJ., Nahabedian MY. The evolution from subcutaneous to prepectoral prosthetic breast reconstruction. *Plast Reconstr Surg Glob Open.* 2018, 6(6): e1797.

36. Ho G., Nguyen TJ., Shahabi A., et al. A systematic review and meta-analysis of complications associated with acellular dermal matrix-assisted breast reconstruction. *Ann Plast Surg.* 2012, 68(4): 346–356.

37. Hallberg H., Lewin R., Søfteland MB., et al. Complications, long-term outcome and quality of life following Surgisis® and muscle-covered implants in immediate breast reconstruction: a case-control study with a 6-year follow-up. Eur *J Plast Surg.* 2019, 42: 33–42.

38. Thakurani S., Gupta S. Evolution of aesthetic surgery in India, current practice scenario, and anticipated post-COVID-19 changes: a survey-based analysis. *Eur J Plast Surg.* 2020, 1–10.

39. Shi Y-D., Qi F-Z., Feng Z-H. Bilateral reduction mammoplasty after heart transplantation. *Heart Surg Forum.* 2014, 17(4): E224–E226.

40. Zellner E., Lentz R. Complications following plastic surgery in solid organ transplant recipients: a descriptive cohort study. *J Aesthet Reconstr Surg.* 2016, 2: 10.

41. Özkan B., Albayati A., Eyüboğlu AA., et al. Aesthetic surgery in transplantation patients: a single center experience. *Exp Clin Transplant.* 2018, Suppl 1(Suppl 1): 194–197.

42. Pan Y., Grindstaff A., Cassada D., et al. Bilateral reduction mammoplasty in a patient treated with calcium channel blocker and cyclosporine after renal transplant: a case report. *Transplantation.* 1997, 63(7): 1032–1033.

Horacio F. Mayer, MD, FACS
Perón 4190 (1181), 1st. floor
Buenos Aires
Argentina
horacio.mayer@hospitalitaliano.org.ar

Submitted: 2. 5. 2021
Accepted: 24.7.2021

doi: 10.48095/ccachp2021113

Characteristics of fingertip injuries and proposal of a treatment algorithm from a hand surgery referral center in Mexico City

J. E. Telich-Tarriba[1], I. Santos-Gallegos[2], C. Arroyo-Berezowsky[3], A. Cardenas-Mejia[1]

[1] Plastic and Reconstructive Surgery Division, Hospital General "Dr Manuel Gea Gonzalez", Postgraduate Division of the Medical School, Universidad Nacional Autonoma de Mexico, Mexico City, Mexico
[2] Universidad de las Americas Puebla School of Medicine, Puebla City, Mexico
[3] Center for Orthopedics and Traumatology, Centro Medico ABC, Mexico City, Mexico

Summary

Background: Fingertips are the most commonly injured anatomical structures in the upper extremity. The aim of this work is to present our experience in the management of fingertip injuries. **Methods:** All patients with fingertip injuries managed by Plastic and Reconstructive Surgery Division of Hospital General "Dr Manuel Gea Gonzalez" in Mexico from July 2010 to June 2015 were included; their demographic characteristics were described, as well as patterns of injury and management. **Results:** A total of 1,265 patients were included in the study, 75% were males. The mean age of presentation was 20.5 ± 16.46 years; the age group most commonly affected was younger than 15 years (46.7%). Right and left-sided injuries were almost equally prevalent (51 vs. 49%). The most commonly injured fingers were the third (27.2%), and second (25.8%). Eighty-seven percent of the patients presented with single-digit injuries. Fingertip amputations were the most common type of injury with 620 cases (49%), followed by simple fingertip lacerations (574 cases, 45%), and nail bed injuries in 71 cases (5.6%). Surgical management was necessary in 95.8% of the cases. **Conclusions:** Fingertip injuries remain the most common reason for consultation in hand emergencies. A structured approach for their treatment is necessary to obtain the best clinical outcomes.

Keywords

fingertip injuries – trauma – Mexico – amputation – lacerations – cross-sectional studies – upper extremity – hand

Telich-Tarriba JE., Santos-Gallegos I., Arroyo-Berezowsky C., et al. Characteristics of fingertip injuries and proposal of a treatment algorithm from a hand surgery referral center in Mexico City. Acta Chir Plast. 2021, 63(3): 113–117.

Background

Fingertips are the most commonly injured anatomical structures of the upper extremity. Their distal location, wide range of movement, and lack of protective structures make them prone to accidents [1]. Over 3 mil. cases are reported annually in the United States [2]. Information regarding their incidence and prevalence in Mexico is lacking, but suspected to be high.

The fingertips are specialized structures that contribute to fine motor control and tactile sensation, they also possess an esthetic value despite their small size. Although fingertip injuries do not represent a risk to a patient's life, adequate evaluation and management are necessary to avoid the development of chronic pain, disability, limitation of social and work activities, or psychological stress [3,4].

Management strategies for fingertip injuries are still debated. International literature is comprised mainly by retrospective, non-comparative studies that present a wide range of recommendations: from coverage with semi-occlusive dressings to supermicrosurgical replantation [5].

Most of the published information comes from developed countries, therefore some treatment strategies do not adjust well to the economic capabilities or sociocultural values of developing nations [6]. Despite this, reconstructive strategies in this group of patients should focus in obtaining a stable skin envelope, minimization of pain, optimization of healing time, preservation of sensitivity and length, prevention of painful neuromas, avoidance of nail deformity, decrease in time lost from work, and providing an acceptable cosmetic appearance [2].

The "Dr Manuel Gea Gonzalez" General Hospital is a tertiary medical facility that provides care mostly to low-income uninsured patients of the southern and eastern areas of Mexico City, amounting to a target population of 2.5 mil. people. It is also recognized as a national referral center for plastic and hand surgery [7]. The aim of this work is to present our ex-

perience in the management of fingertip injuries.

Methods

A retrospective, cross-sectional study was performed to identify the prevalence of fingertip injuries and their treatment strategies. Data was obtained using written and photographic records from the Plastic and Reconstructive Surgery Department of the "Dr Manuel Gea Gonzalez" General Hospital in Mexico City.

Every patient with a fingertip injury, defined as any form of trauma affecting the portion of the finger distal to the insertion of the flexor *digitorum superficialis* and extensor tendons on the distal phalanx, or the interphalangeal joint when referring to the thumb, managed by a plastic surgeon in the emergency department between July 2010 and June 2015 was included in the study.

Full approval by the institutional ethics board was received. Consent was obtained from all patients or their guardians prior to any procedures, and all procedures were in accordance with the ethical principles of the Declaration of Helsinki.

Information was recorded using a data sheet including the following information: patients' demographic characteristics, anatomical location of the lesion (finger, right or left side affected), type of injury (laceration, amputation or nail-bed injury), and type of treatment (conservative or surgical).

Statistical analysis

Descriptive analyses of patient demographic and clinical characteristics were performed. Continuous variables are expressed in central tendency measures, and categorical values are presented as percentages.

Results

During the 5-year period, a total of 1,265 patients presented with fingertip injuries. Seventy-five percent of the patients were males, resulting in a male-to-female ratio of 3 : 1. Mean age of presentation was 20.5 ± 16.46 years. Subsequently, age distribution was classified into 5 groups: 591 patients (46.7%) were younger than 15 years, 330 (26.0%) patients were 16–30 years, 185 (14.6%) were 31–45 years, 119 (9.4%) were 46–60 years, and 40 (3.1%) were older than 61 years of age. Right and left-sided injuries were almost equally prevalent (51 vs. 49%). The most commonly injured finger was the middle (27.2%), followed by the index finger (25.8%), the ring finger (20.7%), the thumb (17.7%) and the small finger (8.7%). Eighty-seven percent of the patients presented with single-digit injuries, 10.7% had injuries in two fingers, and the rest had lesions in three or more digits (Tab. 1).

Tab. 1. Demographic characteristics of the population.

Characteristics	N	%
Sex		
male	946	75
female	319	25
Age groups		
< 15	591	46.7
16–30	330	26.0
31–45	185	14.6
46–60	119	9.4
> 60	40	3.1
Affected finger		
thumb	208	17.7
index	304	25.8
middle	320	27.2
ring	244	20.7
little	102	8.7

Fingertip amputations were the most common type of injury with 620 cases (49%), followed by simple fingertip lacerations (574 cases, 45%), and nail bed injuries in 71 cases (5.6%). Seventy-six patients (6%) suffered from distal phalanx fractures, evidenced by X-ray imaging. Ninety-five percent of the patients required invasive procedures, 99.5% were performed under local anesthesia in a specialized operating room in the emergency department, while the remaining cases were hospitalized and operated in the main operating theaters under general or regional anesthesia.

Allen's classification was used for fingertip amputation. Type 3 lesions were the most prevalent (35.6%), closely followed by type 2 (33.1%), types 1 (17.6%) and 4 (13.7%). Most cases were managed by primary closure (370 patients, 59.6%), 188 patients (15%) required homodigital advancement flaps, regional flaps were performed in 31 patients (5%) and healing by secondary intention was indicated in 28 cases (4.5%). No fingertip replantation was attempted in this series.

Fingertip lacerations were managed by simple primary closure in 192 cases (33.5%), primary closure and nail bed repair in 367 patients (63.9%) and healing by secondary intention in the remaining cases (2.6%).

Simple nail-bed injuries were repaired in 62 cases (86.1%), and managed conservatively in 9 patients (12.6%). Distal phalanx fractures were reduced and fixed with a K-wire in 62 cases (81.5%), all other cases were managed conservatively (14, 18.4%) (Tab. 2).

Discussion

Fingertips are critical structures for hand function, specially fine motor control and sensitivity. Therefore it is important for plastic, orthopedic and hand surgeons to be familiar with the reconstructive strategies developed for this anatomical structures. Fingertip injuries are a frequent cause of consultation in emergency departments. In our study, similar to other published series, fingertip injuries are the most common type of upper extremity trauma [8].

To this day, there is a considerable debate regarding optimal management of fingertip injuries. Few management rec-

Tab. 2. Frequency of each type of injury, and treatment strategies applied.

Injury	N	%
Fingertip laceration	**574**	**45**
primary closure	192	33.5
primary & nail bed repair	367	63.9
secondary intention	15	2.6
Nailbed injury	**71**	**6**
nailbed repair	62	86.1
secondary intention	9	12.6
Fingertip amputation	**620**	**49**
primary closure	383	61.7
advancement flaps	188	30.3
regional flaps	33	5.3
secondary intention	16	2.5
Allen Type I	**109**	**17.6**
primary closure	67	61.4
advancement flaps	24	22.0
regional flaps	4	3.6
secondary intention	14	12.8
Allen Type II	**205**	**33.1**
primary closure	127	61.9
advancement flaps	73	35.6
regional flaps	4	1.9
secondary intention	1	0.4
Allen Type III	**221**	**35.6**
primary closure	135	61.0
advancement flaps	66	29.8
regional flaps	19	8.5
secondary intention	1	0.4
Allen Type IV	**85**	**13.7**
primary closure	54	63.5
advancement flaps	25	29.4
regional flaps	6	7.0
secondary intention	0	0

ommendations are evidence-based, and there is a lack of prospective, comparative trials to guide treatment [5]. Several factors must be considered prior to selecting any treatment modality, such as trauma mechanism, wound geometry and size, patient's age, comorbidities and occupation. Nevertheless, reconstructive goals should focus in obtaining stable skin coverage, optimization of healing time, preservation of sensitivity and length, prevention of painful neuromas, avoiding or limiting nail deformity, minimizing time lost from work, and providing an acceptable cosmetic appearance [1,9].

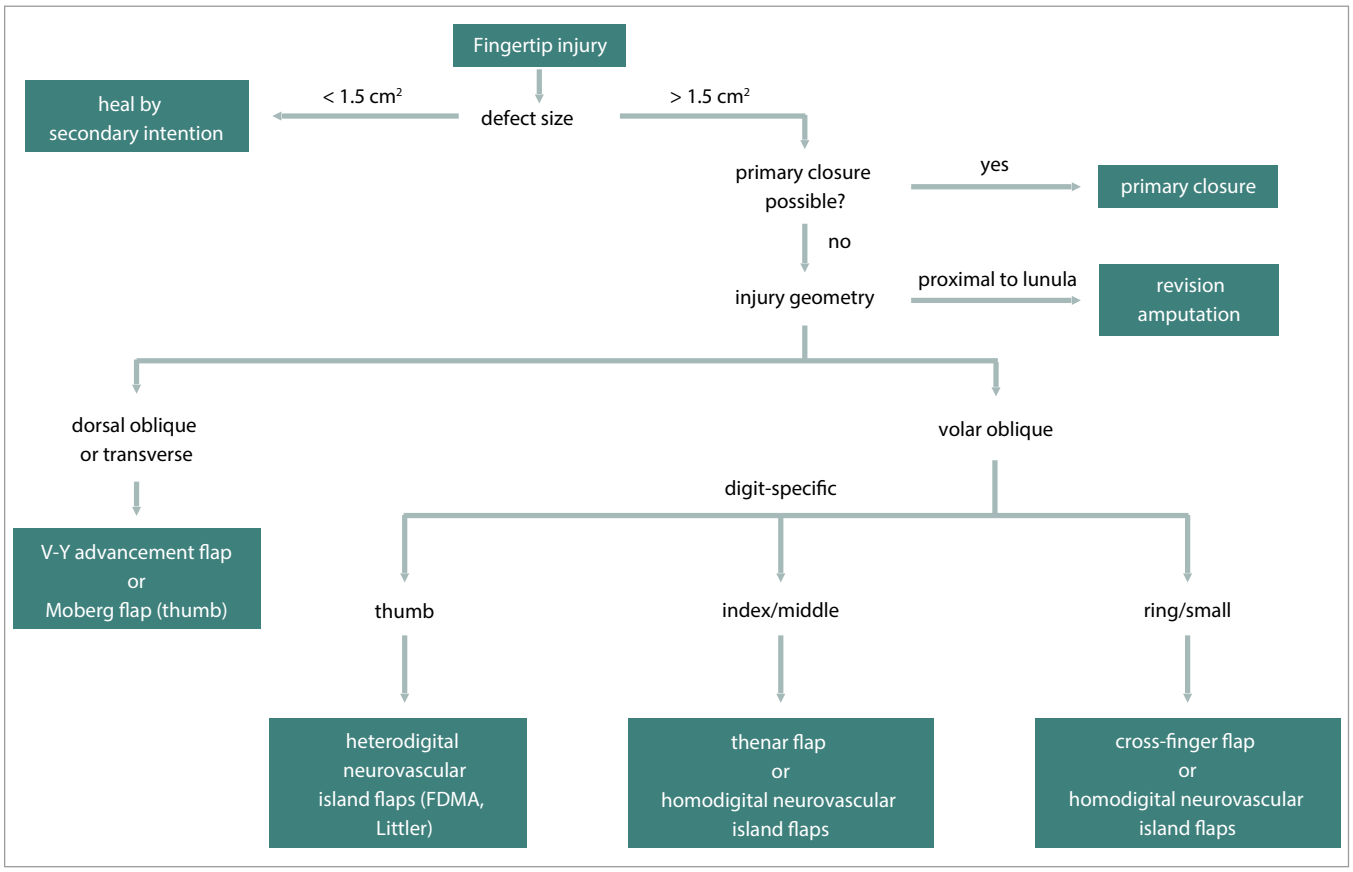
The male-to-female ratio in our population was 3 : 1, these results are similar to other reports, and may reflect the predominance of male workers involved in manufacturing and service jobs in emerging economies [10]. Unlike what is seen in global upper extremity trauma, where economically active people are the largest affected group, almost half of all fingertip injuries were seen in minors. This is relevant due to the added complexity that results from operating smaller structures in potentially uncooperative patients, and the degree of physical and economical burden the development of disability can cause for the patients or their families [7].

Most of our patients were treated using simple surgical procedures such as primary closure or local flap advancement. An incentive for this conduct stems from the fact that our patients tend to be uninsured manual laborers with low-income. Therefore they often ask for a quick return to work and tend to reject procedures requiring hospitalization, such as complex flaps or replantation.

Although replantation seems an ideal method for the treatment of fingertip amputation it is not routinely performed in the Americas, as opposed to Asian countries. Some reasons for this include the risk for replantation failure, need for skillful microsurgical technique, long intraoperative time, prolonged hospital stay, longer time off from work, and higher costs [11–13].

Recent evidence has come to question whether complex reconstructive procedures are worth the time, expense, and risk. For example Wang et al found no outcome differences when comparing complex reconstructions to bone shortening and primary closure, or secondary healing. Meanwhile a survey study by Miller et al found that wound care, stump remodeling or flap advancement were the preferred treatment options by US and international hand surgeons [5,14,15], mirroring our results.

A structured approach to fingertip reconstruction greatly improves



Scheme 1. Proposed algorithm for the management of fingertip injuries [16].
FDMA – first dorsal metacarpal artery

management, specially in academic centers. In 2008 Lemmon et al [16] proposed a treatment algorithm based on characteristics of the injury and the digit affected. We further simplified this algorithm to rely in basic procedures like local and regional random flaps, making it accessible to surgeons of varying levels of skill and knowledge (Scheme 1). This algorithm also fits the sociocultural needs of our patients allowing for quick recovery and minimal downtime. We strongly believe that our results can be applied to other urban areas internationally, especially in developing nations with similar health systems as ours.

Despite our results, it should be taken into account that several interventions in the reconstructive armamentarium remain valuable, and in some cases may deliver better results in aspects like sensitivity, such as regional neurovascularized flaps. Surgeons should proceed with reconstruction only after a thoughtful discussion with the patient and then perform the procedure with which he or she is most comfortable.

The main limitations of this study are its retrospective nature and lack of long-term outcome reports. However, it represents the first step in establishing an epidemiological and demographic registry of fingertip patterns of injury and their management in Mexico.

Conclusions

Fingertip injuries remain the most common reason for consultation in hand emergencies. Even though most cases can be adequately solved by primary closure it is important that the reconstructive team in charge of these patients follow a structured approach for their treatment and is familiar with the several treatment strategies available, in order to obtain the best clinical outcomes.

Role of authors: All authors have been actively involved in the planning, preparation, analysis and interpretation of the findings, enactment and processing of the article with the same contribution.

Disclosure: The authors declare there are no conflicts of interest regarding the publication of this article.

Sources of funding: None declared.

References

1. Peterson SL., Peterson EL., Wheatley MJ. Management of fingertip amputations. *J Hand Surg Am.* 2014, 39(10): 2093–2101.
2. Weichman KE., Wilson SC., Samra F., et al. Treatment and outcomes of fingertip injuries at a large metropolitan public hospital. *Plast Reconstr Surg.* 2013, 131(1): 107–112.
3. Gonzalez C., San-Miguel R. Lesiones traumáticas de la mano. Estudio epidemiológico. *Rev Mex Ortop Traum.* 2001, 15(5): 230–234.
4. Hacıkerim Karşıdağ S., Ozkaya O., Uğurlu K., et al. The practice of plastic surgery in emergency trauma surgery: a retrospective glance

at 10,732 patients. *Ulus Travma Acil Cerrahi Derg.* 2011, 17(1): 33–40.
5. Miller AJ., Rivlin M., Kirkpatrick W., et al. Fingertip amputation treatment: a survey study. *Am J Orthop (Belle Mead NJ).* 2015, 44(9): E331–E339.
6. Torres-Fuentes CE., Hernandez-Beltran JA., Castañeda-Hernandez DA. Manejo inicial de las lesiones de punta de dedo: guía de tratamiento basado en la experiencia en el Hospital San José. *Rev Fac Med.* 2014, 62(3): 335–363.
7. Telich-Tarriba JE., Velazquez E., Theurel-Cuevas A., et al. Upper extremity patterns of injury and management at a Plastic and Reconstructive Surgery Referral Center in Mexico City. *Ann Plast Surg.* 2018, 80(1): 23–26.
8. Sorock GS., Lombardi DA., Hauser RB., et al. Acute traumatic occupational hand injuries: type, location, and severity. *J Occup Environ Med.* 2002, 44(4): 345–351.
9. Germann G., Rudolf KD., Levin SL., et al. Fingertip and thumb tip wounds: changing algorithms for sensation, aesthetics, and function. *J Hand Surg Am.* 2017, 42(4): 274–284.
10. Instituto Nacional de Estadística Geografía e Informática. Indicadores de ocupación y empleo al cuarto trimestre de 2016 [online]. Available from: http://www3.inegi.org.mx/sistemas/temas/default.aspx?s=est&c=25433&t=1.
11. Hattori Y., Doi K., Sakamoto S., et al. Fingertip replantation. *J Hand Surg Am.* 2007, 32(4): 548–555.
12. Maroukis BL., Shauver MJ., Nishizuka T., et al. Cross-cultural variation in preference for replantation or revision amputation: Societal and surgeon views. *Injury.* 2016, 47(4): 818–823.
13. Nishizuka T., Shauver MJ., Zhong L., et al. A comparative study of attitudes regarding digit replantation in the United States and Japan. *J Hand Surg Am.* 2015, 40(8): 1646–1656.
14. Weichman KE., Wilson SC., Samra F., et al. Treatment and outcomes of fingertip injuries at a large metropolitan public hospital. *Plast Reconstr Surg.* 2013, 131(1): 107–112.
15. Wang K., Sears ED., Shauver MJ., et al. A systematic review of outcomes of revision amputation treatment for fingertip amputations. *Hand (N Y).* 2013, 8(2): 139–145.
16. Lemmon JA., Janis JE., Rohrich RJ. Soft-tissue injuries of the fingertip: methods of evaluation and treatment. An algorithmic approach. *Plast Reconstr Surg.* 2008, 122(3): 105e–117e.

José E. Telich-Tarriba, MD
Plastic and Reconstructive Surgery Division
Hospital General "Dr. Manuel Gea Gonzalez"
Av. Calzada de Tlalpan 4800
Tlalpan, Mexico city, 14080
Mexico
e-mail: josetelich@gmail.com

Submitted: 27. 4. 2021
Accepted: 24. 7. 2021

doi: 10.48095/ccachp2021118

Platelet-rich plasma improves esthetic postoperative outcomes of maxillofacial surgical procedures

Y. Menchisheva[1], U. Mirzakulova[1], D. Usupova[2], G. Yermukhanova[3], Z. Rysbayeva[4]

[1] Department Surgical Dentistry, State Hospital №5, S. D. Asfendiyarov Kazakh National Medical University, Almaty, Kazakhstan
[2] Department of the Diseases and Traumatology of the Maxillofacial Region, Tashkent State Dental Institute, Tashkent, Uzbekistan
[3] Department of Pediatric Dentistry, S. D. Asfendiyarov Kazakh National Medical University, Almaty, Kazakhstan
[4] Department of Clinical Disciplines, Al Farabi Kazakh National University, Almaty, Kazakhstan

Summary

Background: Postoperative facial scars after plastic and reconstructive surgery are visible results that can seriously affect the quality of life of recovering patients. Currently, platelet-rich plasma (PRP) is widely used in medicine to improve tissue regeneration. **Purpose:** To analyze the esthetic outcomes of using PRP in the late postoperative period of maxillofacial surgical interventions. **Material and methods:** A total of 100 patients aged 18–60 years who were undergoing plastic and reconstructive surgery in the maxillofacial region were included in this study. The patients were randomly divided in two groups. Fifty patients in the treatment group received PRP injections at the time of surgery. Patients in the control group did not receive any injections. PRP was injected intradermally after suturing the wound. Evaluation of treatment outcomes was carried out by planimetry, the Image J programme during 1 month after surgery and by the Patient and Observer Scar Assessment Scale 30 and 90 days after the surgical procedure. The Dermatological Quality of Life Index was used to assess the negative impact of treatment outcomes on various aspects of the patient's life. **Results:** The change of scar width was twice less pronounced in the treatment group. The patients in the treatment group were more satisfied with the results of the treatment and had a higher quality of life. The treatment group exhibited less scaring at all time points than the control group 3 months after surgery. **Conclusions:** The use of PRP had a pronounced beneficial therapeutic effect in influencing the esthetic outcomes of surgical interventions.

Key words

platelet-rich plasma – scars – quality of life – plastic surgery – outcome measurement

Menchisheva Y., Mirzakulova U., Usupova D., et al. Platelet-rich plasma improves esthetic postoperative outcomes of maxillofacial surgical procedures. Acta Chir Plast. 2021, 63(3): 118–126.

Introduction

Platelet-rich plasma (PRP) is the fraction of plasma containing higher concentrations of platelets compared to whole blood [1]. The platelets are rich in growth factors which boosts healing and repair process [2]. Growth factors contained in PRP – platelet-derived growth factor (PDGF), transforming growth factor β (TGF-β), vascular endothelial growth factor (VEGF or PDAF), insulin-like growth factor (IGF) and epidermal growth factor (EGF) – activate cells migration, stimulate fibroblasts, osteoblasts, endothelial cells and keratinocytes proliferation, enhance the production of collagen and fibronectin, increase vascular permeability and stimulate angiogenesis [3].

PRP is widely applied in different clinical applications to promote healing of damaged tissues. Most of the studies described in the literature are devoted to the use of PRP in traumatology and sports medicine (repairing of acute muscle, tendon, ligament, nerve and cartilage injury and relieve pain in tendonitis, arthritis, ligament sprains and tear) [4–7], gynecology (use of PRP in vulvar lesions, genital prolapse and genital fistulas, in gynesthetics treatment) [8,9], surgery (healing of acute and chronic wounds, burns, defects) [10,11], neurosurgery (treatment of disc tissue pathology, spinal cord injury) [12,13], ophthalmology (treatment of symptomatic dry eye, corneal ulcers and ocular burns) [14,15], dentistry and oral surgery (healing after tooth extraction, treatment of periodontitis, use in implantology) [16,17]. PRP is used in dermatology for purposes including the treatment of ulcers, scars, and alopecia [18].

Thus, the clinical use of PRP is treatment of soft tissue injuries, burns and hard to heal wounds. Also, PRP might be applied to initiate repair of bone lesion in case of reduced osteoblasts proliferation or delayed chondrogenesis [19].

According to the results of conducted studies [1–19] of the use of PRP in surgery and other specialties of medicine, the application of autologous platelet-rich plasma is indicated for the induction of normal wound healing, for promoting the healing of hard to heal or non-healing wounds, ulcers and burns.

Due to the widespread use of PRP in esthetic medicine, plastic surgery and dermatology, it is reasonable to believe that the use of PRP is also indicated for improving the results of surgical treatment.

After plastic and reconstructive surgery, postoperative facial scars have a substantial impact on the quality of life through psychological distress and depression, which affects patients' working capacity and social adaptation [20,21].

Platelet-rich plasma (PRP) releases numerous growth factors that may be invaluable in treatment [22,23]. The effects of growth factors may be beneficial as a therapy for wounds with delayed healing [24,25]. Complications in the early postoperative period, such as suppuration of the wound, divergence of sutures and delayed healing of patients with comorbid conditions often lead to adverse outcomes with scarring in the late postoperative period. Previous studies have assessed the efficiency of PRP in wound healing [26,27] although few of them provide an assessment of the influence on the skin or shed light on patient satisfaction. To evaluate esthetic outcomes, there is a tendency for physicians to use questionnaires [28–30]. In some studies, outcomes are presented with the use of pictures but without objective analysis of quantitative data, or samples are presented too indistinctly to be verifiable and trustworthy. The aim of this study was to evaluate surgical outcomes and esthetic effects in patients after plastic and reconstructive surgery in the maxillofacial area.

Wound healing studies have demonstrated that scars usually develop 6–8 weeks following re-epithelization, and that a period of 6–18 months is required for scar maturation [31,32]. Healing and remodeling are largely complete by 8–12 months [33], and the evaluation of the scars might be delayed until 1-year post-surgery [34]. Therefore, to draw an appropriate conclusion, observation time is critical.

Study hypothesis: esthetic outcomes and the quality of life are better in patients whose surgical incision was injected with PRP.

Material and methods

Patients

One hundred hospital patients aged 18–60 years (City Hospital 5, Almaty, Kazakhstan) who were undergoing plastic and reconstructive surgery in the maxillofacial region and were considered to be at high risk for scaring were included in this randomized controlled trial. Patients were randomly allocated into two groups. Fifty patients (26 males and 24 females aged 43 ± 6 (21–60) years) in the treatment group received PRP injections at the time of surgery, whereas 50 patients (27 females and 23 males aged 41 ± 5 (19–60) years) in the control group did not receive any injections. The patients underwent the following soft tissue procedures (Tab. 1).

All enrolled patients signed informed consent forms to be eligible for research purposes. This randomized controlled trial was based on the revised CONSORT statement [35]. The study is pre-registered in clinical trials registry.

The inclusion criteria were for patients undergoing plastic and reconstructive operation in the maxillofacial area with high risk for scaring. Exclusion criteria were used for patients with platelet dysfunction syndrome, haemodynamic instability, local infection at the site of the procedure, systemic use of corticosteroids within 2 weeks, recent fever, and cancer. To identify patients considered to be at high risk for scaring, we used regression analysis of the results of clinical and laboratory research methods. By the stepwise logistic regression, we identified factors that significantly increase the risk for scaring after surgical procedures (Tab. 2). All factors were obtained during the study of archival material of medical cases of the patients (with and without excessive scaring) who had plastic and reconstructive procedures.

The resulting logistic regression equation for predicting the risk for scaring in the postoperative period is the following:

$$P = \frac{1}{1 + e^{-d}}$$

where d is the value of the discriminant function: d= 2.033 + 1.531× hypertension, ischemic heart disease + 1.051×

Tab. 1. Distribution of patients with postoperative wounds of soft tissues of the maxillofacial region after reconstructive plastic and esthetic operations (N = 100) depending on the type of the operation performed.

	Control group (N = 50)		Treatment group (N = 50)	
	number of patients	%	number of patients	%
flap surgery	30	60	31	62
scar revision surgery	12	24	13	26
secondary cheilorhinoplasty	6	12	4	8
facelift	1	2	1	2
lipofilling	1	2	1	2
total	50	100	50	100

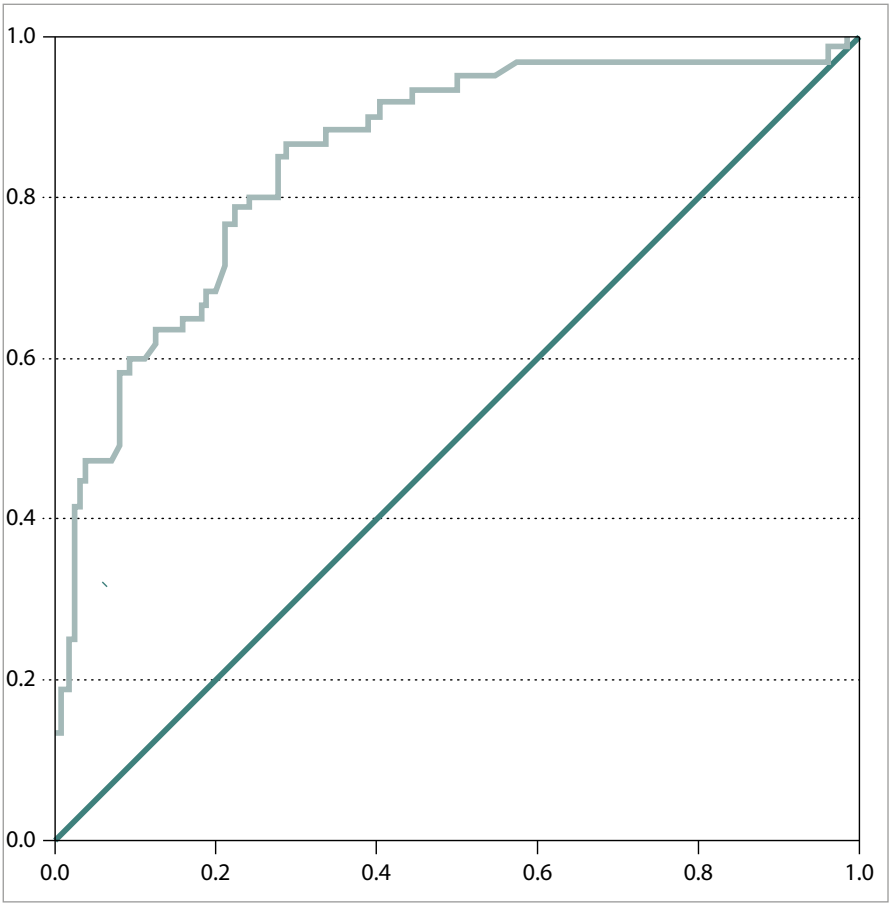
diabetes + 0.239 × the volume of the operation + 0.878 × multiplicity of previous operations – 0.129 × excess of subcutaneous fat – 0,045 × age – 0.021× blood coagulability – 0.018 × gender – 0.014 × the absolute number of platelets in the blood.

If the P-value is < 0.5, then it can be assumed that the "event" (the development for scaring) will not occur; otherwise, an increased risk for scaring is assumed.

To assess the effectiveness of the method for predicting the development of high risk for scaring, the receiver operating characteristic (ROC) analysis was performed with the construction of a ROC curve. The value of the area under the ROC-curve was 0.98 (95% confidence interval), which indicates the informativeness of the proposed forecasting method based on logistic regression (Graph 1).

Tab. 2. Coefficients of the discriminant function of factors contributing to the development of scaring in patients after plastic and reconstructive surgery.

No.	Factors contributing to the development of scaring	Discriminant function coefficients
1	hypertension, ischemic heart disease	1.531
2	diabetes	1.051
3	multiplicity of previous operations (at the same area)	0.878
4	volume of the operation (duration of the operation > 2 hours, the length of the incision > 10 cm)	0.252
5	excess of subcutaneous fat	–0.129
6	age (> 35 years)	–0.045
7	blood coagulability	–0.021
8	gender (women)	0.018
9	absolute number of platelets in the blood	–0.014
10	constant (a)	2.033



Graph 1. Receiver operating characteristic curve.

PRP preparation and method of injection

All patients in the treatment group received PRP during their surgical operations to improve the healing of postoperative soft tissue wounds in the maxillofacial area. Vacuum tubes (9–27 mL) were used for venous blood sampling. On average, one tube of 9 mL was required for wounds < 10 cm in length, two tubes for 10–20 cm wounds, and three tubes for large wounds (> 20 cm). The tubes filled with venous blood were centrifuged for 5 minutes at 3,000 rpm. Thereafter, two fractions of blood samples were visible in the tubes: an erythrocyte-leukocyte clot, and a layer of plasma enhanced with platelets. The lower third of the plasma layer contained 600,000 platelets, the middle of the layer 200,000 platelets, and the top of the layer 50,000 platelets per 1 µL. A syringe was used to take the lower third of the plasma layer, which was injected intradermally, 0.5 cm from the edge of the wound after suturing. Injections of autologous plasma (0.1–0.2 mL) were performed with a syringe using a 30G needle. The distance between injections was 1.5–2 cm. The remaining plasma was applied to a sterile gauze and put over the postoperative wound.

The treatment of patients in the control group was identical to that of patients in the treatment group in the postoperative period and included the following: daily dressings with antiseptic solutions, antibacterial therapy and administration of analgesics.

Evaluation methods

All patients in the treatment and control groups underwent planimetry to determine the width of postoperative scars 1, 3, 5, 7, 10, 30 and 90 days after surgery using a micrometer and Image J program. To record the width of wounds, photographs were taken using a Nikon camera (D5100, 50 mm lens).

The assessment of postoperative scars was carried out after 30 and 90 days by conducting a questionnaire that used the Patient and Observer Scar Assessment Scale (POSAS) with all patients and doctors. The POSAS questionnaire has 6 indicators using a 1–10 scoring scale, with 1 being normal skin and 10 being the least normal skin possible.

The Dermatological Quality of Life Index (DQLI) was used to determine and assess the negative impact of the results of treatment on various aspects of patients' lives 30 and 90 days after surgery. DQLI has 10 questions, with up to 3 points for each question, thus allowing a minimum of 0 points and a maximum of 30 points. A higher score indicates the postoperative scars had a greater negative impact on the patient's quality of life.

The results of histological and ultrasound examination, determination of interleukins in the postoperative wound were published earlier. This study is aimed only at assessing the esthetic component of the results of the use of PRP.

Statistical analysis

The statistical analysis was performed using the SPSS software package (IBM Corp., Released 2012, IBM SPSS Statistics for Windows, Version 21.0, Armonk, NY). The distribution of the parameters was tested using the Kolmogorov–Smirnov method. The variables between two groups were compared by the Mann–Whitney U test as the resultant distribution of parameters in two groups was not normal. The statistical data were presented as the mean with the standard error (SE) and the median with 25–75% limits. The difference of parameters with P value < 0.05 was set as statistically significant. The statistical analysis is performed in consultation with a certified biostatistician from the Department of Biostatistics (S. D. Asfendiyarov KazNMU, Almaty)

Fig. 1. Appearance of scars in patients of the control group on day 10 after surgery.

Fig. 2. Appearance of scars in patients of the control group on day 30 after surgery.

Results

Scars planimetry

Fifty patients in the treatment group and 50 patients in the control group underwent planimetry using a micrometer to determine the width and expansion of postoperative scars. There were no statistically significant differences in the width of postoperative wounds in the first day after the operation.

The median of postoperative wounds width in the control group was 2.0 mm (P_{25} = 1.0; P_{75} = 3.0) which is greater

Fig. 3. Appearance of scars in patients of the treatment group on day 10 after surgery.

Fig. 4. Appearance of scars in patients of the treatment group on day 30 after surgery.

than the median width in the treatment group 1.0 mm (P_{25} = 1.0; P_{75} = 1.5) on 3.5 days after surgery (P < 0.05). On the 7th day after surgical procedure, the median widths of postoperative wounds were 2.0 mm (P_{25} = 1.0; P_{75} = 3.0) and 1,0 mm (P_{25} = 1.0; P_{75} = 2.0) in the control and treatment groups, respectively (P < 0.05).

The most noticeable changes were on the 10th and 30th days after operation. The scars of the patients in the control group (Fig. 1, 2) were distinguishable from the normal surrounding skin on the 10th and 30th days after operation as opposed to the treatment group patients (Fig. 3, 4), who received PRP injections. So, on the 10th day after surgery, the median scar widths were 1.0 mm (P_{25} = 1.0; P_{75} = 2.5) and 2.0 mm (P_{25} = 1.0; P_{75} = 3.0) in the treatment and control groups, respectively (P < 0.05). On the 30th day, this indicator was 3.0 mm (P_{25} = 2.0; P_{75} = 4.0) in the control group, which is greater than the median value of the treatment group – 1.5 mm (P_{25} = 1.0; P_{75} = 3.5) (Graph 2).

Using the Image J program, we measured the width of the scars in pixels on the 10th and 30th days. The median widths of the postoperative scar were 57.6 pixels (P_{25} = 44.0; P_{75} = 92.7) and 62.8 pixels (P_{25} = 46.7; P_{75} = 120.1) in the treatment and control groups on 10th day after surgery, respectively (P < 0.05). One month after the surgical procedure, the postoperative scar width in patients of the treatment group was Me = 80.1 pixels (P_{25} = 47.0; P_{75} = 113.4) which is less than the median of the scar width in patients of the control group Me = 99.3 pixels (P_{25} = 71.1; P_{75} = 130.4), P < 0.05 (Graph 3).

Evaluation of scars

POSAS observer scale

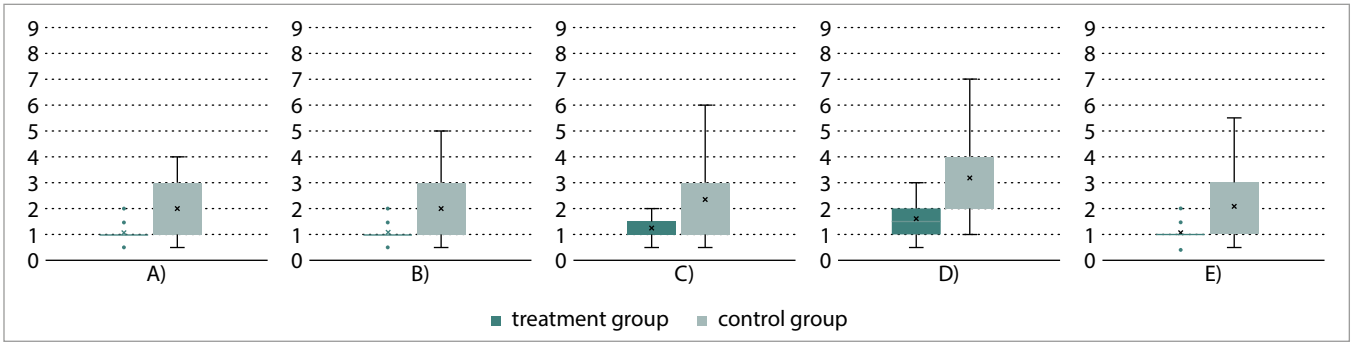
We used the POSAS questionnaire 30 and 90 days after surgery to evaluate the quality of postoperative scars. The POSAS questionnaire (observer part) includes six indicators (vascularity, pigmentation, thickness, relief, pliability, surface area) which were assessed by physicians using a 1–10 scoring scale.

Thirty days after surgery, the mean score value of all six indicators of the scale was 5.8 ± 0.14 in the control group, which was about 2.3× greater than the treatment group mean. The mean value in the treatment group was 2.5 ± 0.14 (P < 0.05). Ninety days after surgery, the mean score value of the control group was 3.7 ± 0.23 and the mean value in the treatment group was 1.6 ± 0.07 (P < 0.05) (Tab. 3).

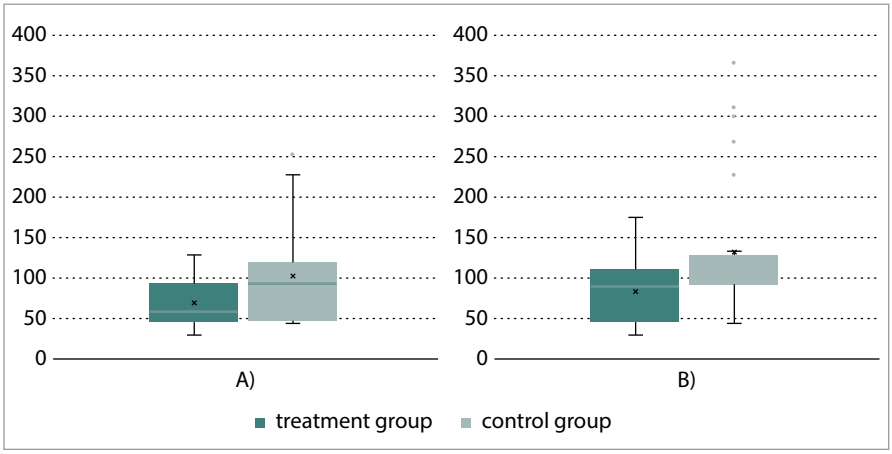
POSAS patient scale

The POSAS questionnaire (patient part) included six questions which were assessed by patients using a 1–10 scoring scale.

Thirty days after surgery, the mean patient POSAS score of the control group was 5.0 ± 0.75, which was about 1.9times greater than the treatment group mean. The mean value in the treatment group was 2.7 ± 0.35 (P < 0.05).



Graph 2. The expansion of postoperative scars (mm) at: A) 3 days; B) 5 days; C) 7 days; D) 10 days; E) 30 days after surgery.



Graph 3. The expansion of postoperative scars (pixels) at: A) 10 and B) 30 days after surgery.

Ninety days after surgery, the mean score value of the control group was 2.7 ± 0.48, which was about 1.8times more than the treatment group mean. The mean value in the treatment group was 1.5 ± 0.14 (P < 0.05). The differences between the mean values in the two groups are displayed in Tab. 4.

Results of the DQLI

Thirty days after surgical procedures, the mean score value in the control group was 12.7 ± 6.7, which was approx. 4times more than in the treatment group, i.e. 3.1 ± 4.25 (P < 0.05). According to the interpretation of DQLI in the control group, the postoperative outcomes of maxillofacial surgical procedures had a strong negative impact on the patients' lives, while in the treatment group, these outcomes had a slight negative impact. Ninety days after surgery, the mean values of scores were 4.3 ± 2.91 and 1.7 ± 1.82 points in the control and treatment groups, respectively (P < 0.05). According to the interpretation in the control group, the treatment results had a slightly negative effect, while in the treatment group, they did not have a negative effect. The differences between the mean values of DQLI on the 30th and 90th days after surgery in the two groups are displayed in Graph 4.

Discussion

The main results of the study are the 2-fold reduction of the scar width on the 90th day after surgery and higher patient satisfaction obtained from questionnaires.

There is a number of studies offering different speed and time of centrifugation to obtain PRP. The methods of preparation of PRP are different in many ways [36–39], which explains the lack of standardized methods of obtainment and application of PRP. The therapeutic effect of PRP could be achieved by increasing the concentration of platelets twice [40]. We were guided by the method of Akhmerov et al [41] in choosing the time and speed of rotation to PRP (specifically 5 min at a speed of 3,000 rpm). Regarding the choice of the frequency of in-

Tab. 3. The mean observer POSAS scores in the control ad treatment groups 30 and 90 days after surgical procedures.

N	Indicators	30 days after surgery					90 days after surgery				
		control group N = 50		treatment group N = 50		P-value	control group N = 50		treatment group N = 50		P-value
		mean ± SE	median (P_{25}–P_{75})	mean ± SE	median (P_{25}–P_{75})		mean ± SE	median (P_{25}–P_{75})	mean ± SE	median (P_{25}–P_{75})	
1.	vascularity	5.6 ± 0.14	7.0 (6.0–7.0)	2.2 ± 0.14	2.0 (1.75–3.0)	P < 0.05	3.0 ± 0.14	3.0 (2.0–4.0)	1.6 ± 0.18	1.0 (1.0–2.0)	P < 0.05
2.	pigmentation	6.4 ± 0.16	7.0 (6.0–7.0)	3.1 ± 0.1	3.0 (2.0–4.0)	P < 0.05	3.8 ± 0.12	4.0 (3.0–4.0)	1.8 ± 0.13	2.0 (1.0–2.0)	P < 0.05
3.	thickness	5.8 ± 0.16	7.0 (6.0–7.25)	2.2 ± 0.14	2.0 (1.75–3.0)	P < 0.05	4.6 ± 0.15	5.0 (4.0–5.0)	1.7 ± 0.18	2.0 (1.0–2.0)	P < 0.05
4.	relief	6.0 ± 0.16	6.5 (6.0–7.0)	2.3 ± 0.13	2.0 (2.0–3.0)	P < 0.05	3.2 ± 0.19	4.0 (3.0–4.0)	1.7 ± 0.16	2.0 (1.0–2.0)	P < 0.05
5.	pliability	6.1 ± 0.16	6.0 (5.75–7.0)	2.5 ± 0.13	2.0 (1.0–2.0)	P < 0.05	4.0 ± 0.16	4.0 (3.0–5.0)	1.6 ± 0.17	2.0 (1.0–2.0)	P < 0.05
6.	surface area	5.4 ± 0.16	6.0 (5.75–7.0)	2.6 ± 0.11	1.5 (1.0–2.0)	P < 0.05	3.6 ± 0.17	4.0 (3.0–5.0)	1.3 ± 0.14	1.0 (1.0–2.0)	P < 0.05

POSAS – patient and observer scar assessment scale

Tab. 4. The mean patient POSAS scores in the control and treatment groups 30 and 90 days after surgical procedures.

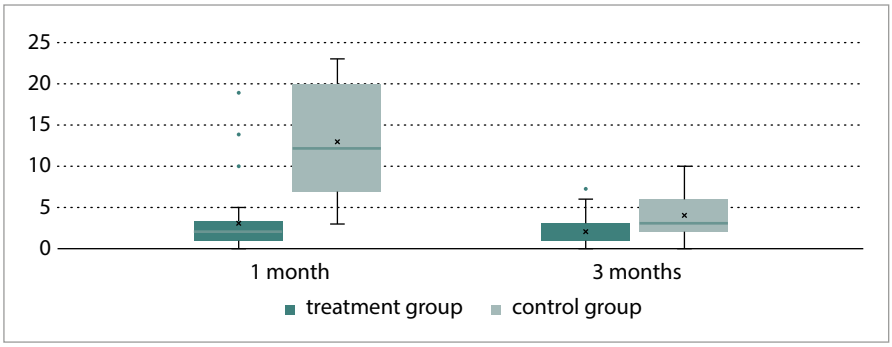
N	Indicators	30 days after surgery					90 days after surgery				
		control group N = 50		treatment group N = 50		P-value	control group N = 50		treatment group N = 50		P-value
		mean ± SE	median (P_{25}–P_{75})	mean ± SE	median (P_{25}–P_{75})		mean ± SE	median (P_{25}–P_{75})	mean ± SE	median (P_{25}–P_{75})	
1.	Has the scar been painful the past few weeks?	2.9 ± 0.13	3.0 (2.0–3.25)	1.4 ± 0.07	1.0 (1.0–2.0)	P < 0.05	1.1 ± 0.05	1.0 (1.0–1.0)	1.0 ± 0.02	1.0 (1.0–1.0)	P < 0.05
2.	Has the scar been itching the past few weeks?	2.5 ± 0.27	3.0 (2.0–4.0)	1.9 ± 0.18	2.0 (1.0–2.0)	P < 0.05	1.3 ± 0.07	1.0 (1.0–2.0)	1.3 ± 0.07	1.0 (1.0–2.0)	P < 0.05
3.	Is the scar color different from the color of your normal skin at present?	6.6 ± 0.23	5.0 (3.0–8.0)	3.3 ± 0.14	2.0 (2.0–3.0)	P < 0.05	3.2 ± 0.14	3.0 (2.0–4.0)	1.9 ± 0.14	2.0 (2.0–3.0)	P < 0.05
4.	Is the stiffness of the scar different from your normal skin at present?	6.0 ± 0.27	6.0 (2.0–8.25)	2.9 ± 0.21	1.0 (1.0–2.25)	P < 0.05	3.2 ± 1.33	3.0 (2.0–4.0)	1.7 ± 0.14	1.0 (1.0–2.25)	P < 0.05
5.	Is the thickness of the scar different from your normal skin at present?	6.6 ± 0.21	6.0 (2.0–7.75)	3.5 ± 0.25	2.0 (1.0–3.25)	P < 0.05	3.7 ± 1.43	4.0 (3.0–5.0)	1.8 ± 0.15	2.0 (1.0–3.25)	P < 0.05
6.	Is the scar more irregular than your normal skin at present?	5.7 ± 0.31	5.0 (2.0–6.0)	3.4 ± 0.23	2.0 (1.0–2.25)	P < 0.05	3.7 ± 1.51	4.0 (2.75–5.0)	1.7 ± 0.12	2.0 (1.0–2.25)	P < 0.05

POSAS – patient and observer scar assessment scale

jection of PRP several studies reported about multiplicity of PRP application [43–45] or injection [46] during or after surgery.

We used a single plasma injection, since we believe that a single plasma injection as a stimulator of regeneration is sufficient to start the process of normal wound healing. A single PRP injection has also been suggested in the studies of Eichler et al [47].

Considering the anatomical features of blood supply and innervation on



Graph 4. The mean values of the dermatological quality of life index in patients of the control and the treatment groups at 1 and 3 months after surgical procedures.

the face and neck, we propose to inject PRP leaving 0.5 cm from the edge of the wound. We were guided by the regulation of the Republic of Kazakhstan (No. 666, November, 2009) on the procurement and processing of blood components, choosing the amount of blood taken from the patient. According to the recommendations of Akhmerov et al [41], in the treatment of various diseases (in such fields of medicine as surgery, traumatology, gynecology), it is necessary to inject 3–9 mL of PRP, depending on the clinical case. A total of 9 mL of blood was required to obtain 3 mL of PRP. In current study, one tube of 9 mL was required for wounds < 10 cm in length (3 mL of PRP), two tubes for 10–20 cm wounds (6 mL of PRP), and three tubes for wounds > 20 cm (9 mL of PRP).

The goal of PRP is to minimize wound complications and attain better esthetic outcomes. Previous studies have shown the efficiency of PRP in different wound healing processes, but few have provided an assessment of the influence of PRP on skin quality or assessed patient satisfaction with treatment results.

Several studies have evaluated the potential of platelet rich plasma to treat scar tissues. Willemsen et al reported that platelet rich plasma reduced recovery time and improved esthetic outcomes in facial rejuvenation [48]. They observed when the patients could return to work or restart their social activities after surgery. The authors conducted questionnaires about the appearance of 82 patients' faces after 4 weeks. They used three questions with a scale 1–10 and surveyed only surgeons. Although they used a different scale than the one used in our study, the results were similar: both studies found that scarring was less pronounced in the treatment group relative to the control group. Our study also surveyed patients. We consider this a strength of our study because a surgeon's perspective alone may not be objective, and because the patient perspective on their scarring is ultimately the most important in relation to patients' quality of life.

Many studies evaluate the use of PRP in combination with other treatment methods. These studies have had very similar designs, often being presented in a couple of groups, where researchers compare results of treatment methods, one of which includes the use of PRP. Majani et al write about the treatment of patients with traumatic scars [49]. In this study which used a small sample size, and the Manchester Scar Scale, it was found that PRP was associated with better treatment results.

It was our aim to find studies not limited to only facial surgeries or dermatology, where authors describe the esthetic results after surgeries. The most extensive study in our search was made by Balbo et al, where a five-year analysis of the results of 115 patients with the amputations or wounds of fingers treated with platelet gel was presented [50]. The difference of this study from the study conducted at our hospital is the application of the platelet rich gel, not the injection of PRP directly into the soft tissues as it was done in our case. Balbo et al reported that the recovery of soft tissues of all patients ranged from 80 to 100% (median time 3 weeks) and the esthetic results were satisfactory in nearly all cases that were shown in numerous photos after surgeries. According to the article, patients who have undergone surgeries were satisfied with the results of the treatment afterwards, but these claims were not supported by objective quantitative data.

None of the studies found in the literature were directly comparable to our study in terms of design or methodology. However, all studies found similar results. A strength of our study was that we measured outcomes from different perspectives (both that of the patient and the surgeon) and triangulated results from different methods of measurement. We feel that this makes our study more objective than those conducted previously.

Conclusion

The current study demonstrates two findings: the first was that the use of PRP improves postoperative wound healing and results in better esthetic outcomes in the postoperative period; the second finding was that the patient satisfaction with the results and quality of life was higher in the treatment group where PRP was used.

Role of authors: Yuliya Menchisheva: originate concept and design of the study, operation of the patients, measurement of the scars, PRP preparation, acquisition, analysis and interpretation of the data, critical revision of the manuscript, crafting of the manuscript.

Ulmeken Mirzakulova: operation of the patients, analysis and interpretation of the data, crafting of the manuscript, statistical analysis.

Dildora Usupova: operation of the patients, measurement of scars of patients, data analysis.

Gulzhan Yermukhanova: review of the literature, critical revision of the manuscript, crafting of the manuscript.

Zhanagul Rysbayeva: review of the literature, crafting of the manuscript, statistical analysis.

Ethical considerations: All participating patients signed informed consent forms to be eligible for research. Ethics approval was obtained from the local ethics Committee. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

Conflict of interest: We are declaring that no competing interests exist. We declare that we received no financial support for the research, authorship or publication of this article.

References

1. Borrione P., Gianfrancesco AD., Pereira MT., et al. Platelet-rich plasma in muscle healing. *Am J Phys Med Rehabil.* 2010, 89(10): 854–861.
2. Chicharro-Alcántara D., Rubio-Zaragoza M., Damiá-Giménez E., et al. Platelet rich plasma: new insights for cutaneous wound healing management. *J Funct Biomater.* 2018, 9(1): 10.
3. Sclafani AP., Azzi J. Platelet preparations for use in facial rejuvenation and wound healing: a critical review of current literature. *Aesth Plast Surg*. 2015; 39(4): 495–505.
4. Hall MP., Band PA., Meislin RT., et al. Platelet-rich plasma: current concepts and application in sports medicine. *J Am Acad Orthop Surg*. 2009, 17(10): 602–608.
5. Li X., Xu C., Hou YL., et al. Are Platelet concentrates an ideal biomaterial for arthroscopic rotator cuff repair? A meta-analysis of randomized controlled trials. *Arthroscopy* 2014, 30(11): 1483–1490.

6. Sanchez M., Delgado D., Sr'anchez P., et al. Platelet rich plasma and knee surgery. *Biomed Res Int*. 2014, 2014: 890630.
7. Creaney L., Hamilton B. Growth factor delivery methods in the management of sports injuries: the state of play. *Br J Sports Med*. 2008, 42(5): 314–320.
8. Dawood AS., Salem HA. Current clinical applications of platelet-rich plasma in various gynecological disorders: An appraisal of theory and practice. *Clin Exp Reprod Med*. 2018, 45(2): 67–74.
9. Galal M., Khalifa A., Abd El Hafez M., et al. Platelet-rich plasma (PRP) in obstetrics and gynecology. Egypt J Hosp Med. 2021, 83(1): 889–894.
10. de Vos RJ., van Veldhoven PL., Moen MH., et al. Autologous growth factor injections in chronic tendinopathy: a systematic review. *Br Med Bull*. 2010, 95: 63–77.
11. Ahmed M., Reffat SA., Hassan A., et al. Platelet-rich plasma for the treatment of clean diabetic foot ulcers. *Ann Vasc Surg*. 2017, 38: 206–211.
12. Ji-Jun H., Hui-Hui S., Qing L., et al. Efficacy of using platelet-rich plasma in spinal fusion surgery-a preferred reporting items for systematic reviews and meta-analyses-compliant meta-analysis. *World Neurosurg*. 2020, 139: e517–e525.
13. Kaplan N. A study of platelet rich plasma commonly used in neurosurgery practice. *Merit Res J Med Sci*. 2019, 7(1): 1–7.
14. Ronci C., Ferraro AS., Lanti A., et al. Platelet-rich plasma as treatment for persistent ocular epithelial defects. *Transfus Apher Sci*. 2015; 52(3): 300–304.
15. Alio JL., Arnalich-Montiel F., Rodriguez AE. The role of "eye platelet rich plasma" (E-PRP) for wound healing in ophthalmology. *Curr Pharm Biotechnol*. 2012, 13(7): 1257–1265.
16. Albanese A., Licata ME., Polizzi B., et al. Platelet-rich plasma (PRP) in dental and oral surgery: from the wound healing to bone regeneration. Immun Ageing. 2013, 10(1): 23.17. Carlson NE., Roach RB. Jr. Platelet-rich plasma: clinical applications in dentistry. *J Am Dent Assoc*. 2002, 133(10): 1383–1386.
18. Khatu SS., More YE., Gokhale NR., et al. Platelet-rich plasma in androgenic alopecia: myth or an effective tool. *J Cutan Aesthet Surg*. 2014, 7(2): 107–110.
19. Oryan A., Alidadi S., Moshiri A. Platelet-rich plasma for bone healing and regeneration. *Expert Opin Biol Ther*. 2016, 16(2): 213–232.
20. De Sousa A. Psychological issues in oral and maxillofacial reconstructive surgery. *Br J Oral Maxillofac Surg*. 2008, 46(8): 661–664.
21. De Sousa A. Psychological issues in acquired facial trauma. *Indian J Plast Surg*. 2010, 43(2): 200–205.
22. Gasparyan AY., Ayvazyan L., Pretorius E., et al. Platelets in rheumatic diseases: friend or foe? *Curr Pharm Des*. 2014, 20(4): 552–566.
23. Cole BJ., Seroyer ST., Filardo G., et al. Platelet-rich plasma: where are we now and where are we going? *Sports Health*. 2010, 2(3): 203–210.
24. Lacci KM., Dardik A. Platelet-rich plasma: support for its use in wound healing. *Yale J Biol Med*. 2010, 83(1): 1–9.
25. Chicharro-Alcántara D., Rubio-Zaragoza M., Damiá-Giménez E., et al. Platelet rich plasma: new insights for cutaneous wound healing management. *J Funct Biomater*. 2018, 9(1): 10.
26. Wang L., Gu Z., Gao C. Platelet-rich plasma for treating acute wounds: a meta-analysis. *Zhonghua Yi Xue Za Zhi*. 2014, 94(28): 2169–2174.
27. Prabhu R., Vijayakumar C., Bosco Chandra AA., et al. Efficacy of homologous, platelet-rich plasma dressing in chronic non-healing ulcers: an observational study. *Cureus*. 2018, 10(2): e2145.
28. Malay S., Chung KC. How to use outcomes questionnaires: pearls and pitfalls. *Clin Plast Surg*. 2013, 40(2): 261–269.
29. Rezaei F., Rezaei F., Abbasi H., et al. A comparison of doctor/patient satisfaction with aesthetic outcomes of rhinoplasty: a prospective study. *J Med Life*. 2019, 12(4): 374–380.
30. Fearmonti R., Bond J., Erdmann D., et al. A review of scar scales and scar measuring devices. *Eplasty*. 2010, 10: e43.
31. Commander SJ., Chamata E., Cox J., et al. Update on postsurgical scar management. *Semin Plast Surg*. 2016, 30(3): 122–128.
32. Marshall CD., Hu MS., Leavitt T., et al. Cutaneous scarring: basic science, current treatments, and future directions. *Adv Wound Care (New Rochelle)* 2018, 7(2): 29–45.
33. Garg S., Dahiya N., Gupta S. Surgical scar revision: an overview. *J Cutan Aesthet Surg*. 2014, 7(1): 3–13.
34. Jourdan M., Madfes DC., Lima E., et al. Skin care management for medical and aesthetic procedures to prevent scarring. *Clin Cosmet Investig Dermatol*. 2019, 12: 799–804.
35. Moher D., Schulz KF., Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. *Ann Intern Med*. 2001, 134(8): 657–662.
36. Breddin HK. Can platelet aggregometry be standardized? *Platelets* 2005, 16(3–4): 151–158.
37. Araki J., Jona M., Eto H., et al. Optimized preparation method of platelet-concentrated plasma and noncoagulating platelet-derived factor concentrates: maximization of platelet concentration and removal of fibrinogen. *Tissue Eng Part C Methods*. 2012, 18(3): 176–185.
38. Dugrillon A., Eichler H., Kern S., et al. Autologous concentrated platelet-rich plasma (cPRP) for local application in bone regeneration. *Int J Oral Maxillofac Surg*. 2002, 31(6): 615–619.
39. Franco D., Franco T., Schettino AM., et al. Protocol for obtaining platelet-rich plasma (PRP), platelet-poor plasma (PPP), and thrombin for autologous use. *Aesth Plast Surg*. 2012, 36(5): 1254–1259.
40. Weibrich G., Hansen T., Kleis W., et al. Effect of platelet concentration in platelet-rich plasma on periimplant bone regeneration. *Bone*. 2004, 34(4): 665–671.
41. Akhmerov RR., Korotkova OI., Ovechkina MV., et al. Use of the autoplazma containing thrombocytes in a dermatokosmetologiya and an odontology. Plasmolifting™ technology. Plastic surgery and cosmetology. *Russian Journal (Plasticheskaya khirurgiya i kosmetologiya)* 2013, 1: 94.
42. Hom DB., Linzie BM., Huang TC. The healing effects of autologous platelet gel on acute human skin wounds. *Arch Facial Plast Surg*. 2007, 9(3): 174–183.
43. Khalafi RS., Bradford DW., Wilson MG. Topical application of autologous blood products during surgical closure following a coronary artery bypass graft. *Eur J Cardiothorac Surg*. 2008, 34(2): 360–364.
44. Kazakos K., Lyras DN., Verettas D., et al. The use of autologous PRP gel as an aid in the management of acute trauma wounds. *Injury* 2009, 40(8): 801–805.
45. Yoo J., Roth K., Hughes B., et al. Evaluation of postoperative drainage with application of platelet-rich and platelet-poor plasma following hemithyroidectomy: a randomized controlled clinical trial. *Head Neck*. 2008, 30(12): 1552–1558.
46. Guo Y., Qiu J., Zhang C. Follow-up study on platelet-rich plasma in repairing chronic wound nonunion of lower limbs in 47 cases. *Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi*. 2008, 22(11): 1301–1305.
47. Eichler C., Najafpour M., Sauerwald A., et al. Platelet-rich plasma in the treatment of subcutaneous venous access device scars: a head-to-head patient survey. *Biomed Res Int*. 2015, 2015: 630601.
48. Willemsen JC., van der Lei B., Vermeulen KM., et al. The effects of platelet-rich plasma on recovery time and aesthetic outcome in facial rejuvenation: preliminary retrospective observations. *Aesthetic Plastic Surg*. 2014, 38(5): 1057–1063.
49. Majani U., Majani A. Correction of scars by autologous fat graft and platelet rich plasma (PRP). *Acta Medica Mediterranea* 2012, 28(2): 99–100.
50. Balbo R., Avonto I., Marenchino D., et al. Platelet gel for the treatment of traumatic loss of finger substance. *Blood Transfus.* 2010, 8(4): 255–259.

Yuliya Menchisheva, MD, PhD
S. D. Asfendiyarov Kazakh National Medical University
Tole bi 94
Almaty, 050000
Kazakhstan
e-mail: menchisheva.y@kaznmu.kz

Submitted: 30. 4. 2021
Accepted: 24. 7. 2021

doi: 10.48095/ccachp2021127

Breast implant-associated anaplastic large-cell lymphoma – an evolution through the decades: citation analysis of the top fifty most cited articles

A. P. Kallarackal[1], I. Slaninka[2], N. Mrozková[3]

[1] *Faculty of Medicine in Hradec Králové, Charles University, Prague*
[2] *Department of Plastic Surgery, Faculty Hospital Hradec Králové*
[3] *Faculty of Pharmacy in Hradec Králové, Charles University, Prague*

Summary

Background: Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) is a recently discovered malignancy of T-cell type, correlated with the use of silicone breast implants. It has been theorized that the etiology may be linked to bacterial growth and long-term inflammation. The afflicted patient usually presents with breast swelling due to peri-implant fluid accumulation. Currently, the diagnosis is achieved by ultrasound, biopsy and testing for certain biomarkers. Following this, the treatment is achieved by complete surgical excision, or by capsulectomy and exchange with smoother surfaced implants. The aim of this study was to identify and report 50 most cited articles related to the field of BIA-ALCL. **Methods:** The Web of Science Citation Index was used to identify 325 articles pertaining to BIA-ALCL. The 50 most cited articles among these were included in this study. The title, author name, journal and year of publication, country and institute of origin, level of evidence (LoE), type of study (clinical or basic), and topic of study (pathophysiology, oncologic management, diagnosis, case report and case series) were recorded. **Results:** This study includes articles from the period 1997–2018 with an average citation rate of 65.5. The majority of the top cited articles (36%; N = 18) were found to be case reports, followed by case series (18%; N = 9), systemic reviews (12%; N = 6) and studies focused on the pathophysiology (16%; N = 8), oncologic management (6%; N = 3), databases (6%; N = 3), diagnostics (4%; N = 2) and informed consent (2%; N = 1). The articles were published across 30 journals and originated from 35 institutes. The United States was found to be the country of origin of most of the studies. While none of the articles achieved LoE 1, many were found to have LoE 4 (N = 11) or 5 (N = 19). Most of the articles (N = 42), were clinical research studies. **Conclusion:** According to this citation analysis, a large fraction of the existing high impact literature on BIA-ALCL is focused on disease monitoring. Through this study, we hope to present a simple educational tool to better appreciate the research in this relatively young field.

Key words

BIA-ALCL – breast implant-associated anaplastic large cell lymphoma – breast implant illness – breast implant lymphoma

Kallarackal AP., Slaninka Y., Mrozková N. Breast implant-associated anaplastic large-cell lymphoma – an evolution through the decades: citation analysis of the top fifty most cited articles. Acta Chir Plast. 2021, 63(3): 127–138.

Introduction

Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) is a newly recognized neoplastic disease entity. As suggested by the nomenclature, this malignancy of T-cell type is strongly linked to the use of breast implants. Though first described in 1997 by Keech and Creech [1], it was only recently that BIA-ALCL has received wider recognition in the medical field. In 2011, it was recognized by FDA [2] and in 2016, it was included in the WHO classification of lymphoid malignancies [3]. The latest studies on etiopathogenesis theorize that textured implants promote the growth of bacteria on them and a subsequent formation of a biofilm, leading to chronic inflammation and malignant transformation.

Over the last decade, there has been increased awareness and improved diagnostics [4] with peri-implant fluid collection and classification of implant shell textures [5] leading to the detection and treatment of an increasing number of cases. As of today, there exists a large array of studies on BIA-ALCL focused on the topics as pathophysiology, diagnostics, oncologic management and reconstruction. Thus, there arises a need to identify the most important articles with a greater impact. In this study, we chose citation analysis as a tool to achieve the

Tab. 1. Top 50 most cited articles in breast implant-associated anaplastic large cell lymphoma.

No	Title	Author	Journal	Total citations	Publication year	Institute	Country
1	Anaplastic large-cell lymphoma in women with breast implants	de Jong et al [10]	JAMA-JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION	189	2008	Netherlands Cancer Institute	Netherlands
2	Anaplastic T-cell lymphoma in proximity to a saline-filled breast implant	Keech JA [1]	PLASTIC AND RECONSTRUCTIVE SURGERY	161	1997	Cooper University Hospital	USA
3	Breast implant-associated anaplastic large-cell lymphoma: long-term follow-up of 60 patients	Miranda et al [11]	JOURNAL OF CLINICAL ONCOLOGY	147	2014	University of Texas MD Anderson Cancer Center	USA
4	Anaplastic large cell lymphoma occurring in women with breast implants: analysis of 173 cases	Brody et al [16]	PLASTIC AND RECONSTRUCTIVE SURGERY	137	2015	University of Southern California, Keck School of Medicine	USA
5	Bacterial biofilm infection detected in breast implant-associated anaplastic large-cell lymphoma	Hu [12]	PLASTIC AND RECONSTRUCTIVE SURGERY	127	2016	Macquarie University	Australia
6	Complete surgical excision is essential for the management of patients with breast implant-associated anaplastic large-cell lymphoma	Clemens et al [14]	JOURNAL OF CLINICAL ONCOLOGY	117	2016	University of Texas MD Anderson Cancer Center	USA
7	Seroma-associated primary anaplastic large-cell lymphoma adjacent to breast implants: an indolent T-cell lymphoproliferative disorder	Roden et al [15]	MODERN PATHOLOGY	111	2008	Mayo Clinic	USA
8	Anaplastic large cell lymphoma and breast implants: a systematic review	Kim et al [17]	PLASTIC AND RECONSTRUCTIVE SURGERY	105	2011	Rand Health and Pardee Rand Graduate School	USA
9	Chronic biofilm infection in breast implants is associated with an increased T-cell lymphocytic infiltrate: implications for breast implant-associated lymphoma	Hu et al [18]	PLASTIC AND RECONSTRUCTIVE SURGERY	102	2015	Macquarie University	Australia
10	Breast implant-associated anaplastic large cell lymphoma in Australia and New Zealand: high-surface-area textured implants are associated with increased risk	Loch-Wilkinson et al [19]	PLASTIC AND RECONSTRUCTIVE SURGERY	98	2017	Macquarie University	Australia
11	Anaplastic large cell lymphoma associated with breast implants: a report of 13 cases	Aladily et al [20]	AMERICAN JOURNAL OF SURGICAL PATHOLOGY	95	2012	University of Texas MD Anderson Cancer Center	USA
12	US epidemiology of breast implant-associated anaplastic large cell lymphoma	Doren et al [21]	PLASTIC AND RECONSTRUCTIVE SURGERY	85	2017	University of Texas MD Anderson Cancer Center	USA

13	Breast implant-associated anaplastic large cell lymphoma: two distinct clinicopathological variants with different outcomes	Laurent et al (22)	ANNALS OF ONCOLOGY	80	2016	Institut Universitaire du Cancer-Oncopole	France
14	CD30+T cells in late seroma may not be diagnostic of breast implant-associated anaplastic large cell lymphoma	Kadin []	AESTHETIC SURGERY JOURNAL	71	2017	Roger Williams Medical Centre, Providence	USA
15	Biomarkers provide clues to early events in the pathogenesis of breast implant-associated anaplastic large cell lymphoma	Kadin et al [13]	AESTHETIC SURGERY JOURNAL	71	2016	Boston University School of Medicine, Boston	USA
16	Breast implants and the risk of anaplastic large-cell lymphoma in the breast	de Boer [24]	JAMA ONCOLOGY	70	2018	VU University Medical Centre, Amsterdam	Netherlands
17	Breast lymphoma associated with breast implants: Two case-reports and a review of the literature	Gaudet et al [25]	LEUKEMIA & LYMPHOMA	67	2002	Dana-Farber Cancer Institute, Boston	USA
18	Anaplastic large cell lymphoma involving the breast a clinicopathologic study of 6 cases and review of the literature	Miranda et al [26]	ARCHIVES OF PATHOLOGY & LABORATORY MEDICINE	64	2009	University of Texas MD Anderson Cancer Center	USA
19	A patient death attributable to implant-related primary anaplastic large cell lymphoma of the breast	Carty et al [27]	PLASTIC AND RECONSTRUCTIVE SURGERY	63	2011	Brigham and Women's Hospital	USA
20	Primary breast lymphoma in a patient with silicone breast implants: a case report and review of the literature	Newman et al [28]	JOURNAL OF PLASTIC RECONSTRUCTIVE AND AESTHETIC SURGERY	59	2008	Virginia Commonwealth University Medical Centre	USA
21	Effusion-associated anaplastic large cell lymphoma of the breast: time for it to be defined as a distinct clinicopathological entity	Thompson et al [29]	HAEMATOLOGICA-THE HEMATOLOGY JOURNAL	58	2010	Peter MacCallum Cancer Centre	Australia
22	Anaplastic large cell lymphoma associated with a breast implant capsule: A case report and review of the literature	Wong [30]	AMERICAN JOURNAL OF SURGICAL PATHOLOGY	58	2008	University of Southern California, Cedars-Sinai Medical Centre	USA
23	Survival signals and targets for therapy in breast implant-associated ALK anaplastic large cell lymphoma	Lechner et al [31]	CLINICAL CANCER RESEARCH	53	2012	Keck School of Medicine, University of Southern California	USA
24	The PIP mammary prosthesis: a product recall study	Berry et al [32]	JOURNAL OF PLASTIC RECONSTRUCTIVE AND AESTHETIC SURGERY	50	2012	Surgical Aesthetics. London	UK
25	Anaplastic large-cell non-Hodgkin's lymphoma of the breast in periprosthetic localisation 32 years after treatment for primary breast cancer - a case report	Fritzsche et al [33]	VIRCHOWS ARCHIV	49	2006	Charité Universitätsmedizin, Berlin	Germany
26	Breast implant-associated, ALK-negative, T-Cell, anaplastic, large-cell lymphoma: establishment and characterization of a model cell line (TLBR-1) for this newly emerging clinical entity	Lechner et al [34]	CANCER	49	2011	USC Kerk School of Medicine LA	USA

27	Silicone implant and primary breast ALK1-negative anaplastic large cell lymphoma, fact or fiction?	Li et al [35]	INTERNATIONAL JOURNAL OF CLINICAL AND EXPERIMENTAL PATHOLOGY	48	2010	Emory Univ. School of Medicine, Atlanta	USA
28	Global adverse event reports of breast implant-associated ALCL: an international review of 40 government authority databases	Srinivasa et al [36]	PLASTIC AND RECONSTRUCTIVE SURGERY	48	2017	University of Texas MD Anderson Cancer Center	USA
29	Breast implant-associated anaplastic large cell lymphoma: a systematic review	Gidengilet al [37]	PLASTIC AND RECONSTRUCTIVE SURGERY	48	2015	Rand Health, Boston	USA
30	Anaplastic large cell lymphoma occurring in association with breast implants: review of pathologic and immunohistochemical features in 103 cases	Taylor et al [38]	APPLIED IMMUNOHISTOCHEMISTRY & MOLECULAR MORPHOLOGY	48	2013	University of Southern California	USA
31	Primary anaplastic large-cell lymphoma associated with breast implants	Popplewell et al [39]	LEUKEMIA & LYMPHOMA	48	2011	City of Hope, National Medical Center, Duarte	USA
32	Anaplastic large cell lymphoma arising in a saline breast implant capsule after tissue expander breast reconstruction	Olack et al [40]	ANNALS OF PLASTIC SURGERY	47	2007	Tufts University school of Medicine, Baystate Medical Centre	USA
33	Aggressive presentation of breast implant-associated ALK-1 negative anaplastic large cell lymphoma with bilateral axillary lymph node involvement	Alobeid et al [41]	LEUKEMIA & LYMPHOMA	46	2009	Columbia Univ, New York	USA
34	Whole exome sequencing reveals activating JAK1 and STAT3 mutations in breast implant-associated anaplastic large cell lymphoma anaplastic large cell lymphoma	Blomber et al [42]	HAEMATOLOGICA	45	2016	Peter MacCallum Cancer Centre	Australia
35	Anaplastic large cell lymphoma and breast implants: five Australian cases	Taylor et al [43]	PLASTIC AND RECONSTRUCTIVE SURGERY	45	2012	Peter MacCallum Cancer Centre	Australia
36	Breast implant-associated anaplastic large cell lymphoma: sensitivity, specificity, and findings of imaging studies in 44 patients	Adrada et al [44]	BREAST CANCER RESEARCH AND TREATMENT	44	2014	University of Texas MD Anderson Cancer Center	USA
37	Primary anaplastic large cell lymphoma of the breast arising in reconstruction mammoplasty capsule of saline filled breast implant after radical mastectomy for breast cancer: an unusual case presentation	Bishara et al [45]	DIAGNOSTIC PATHOLOGY	44	2009	Henderson Hospital, Ontario	Canada
38	Breast implant-associated ALK-negative anaplastic large cell lymphoma: a case report and discussion of possible pathogenesis	George et al [46]	INTERNATIONAL JOURNAL OF CLINICAL AND EXPERIMENTAL PATHOLOGY	43	2013	University of Florida College of Medicine	USA
39	Macrotextured breast implants with defined steps to minimize bacterial contamination arouond the device: experience in 42,000 implants	Adams et al [47]	PLASTIC AND RECONSTRUCTIVE SURGERY	41	2017	University of Texas, Southwestern Medical centre	USA

40	Breast implant-associated anaplastic large cell lymphoma: a systematic review of the literature and mini-meta analysis	Thompson et al [2013]	CURRENT HEMATOLOGIC MALIGNANCY REPORTS	40	2013	Royal Melbourne Hospital, Parkville	Australia
41	Breast implant-associated ALCL: a unique entity in the spectrum of CD30(+) lymphoproliferative disorders	Story et al [49]	ONCOLOGIST	36	2013	University of Pittsburgh	USA
42	Targeted next generation sequencing of breast implant-associated anaplastic large cell lymphoma reveals mutations in JAK/STAT signalling pathway genes, TP53 and DNMT3A	Di Napoli [50]	BRITISH JOURNAL OF HAEMATOLOGY	34	2018	Sapienza University, Sant Andrea Hospital, Rome	ITALY
43	Breast implant informed consent should include the risk of anaplastic large cell lymphoma	Clemens et al [14]	PLASTIC AND RECONSTRUCTIVE SURGERY	34	2016	University of Texas MD Anderson Cancer Center	USA
44	Breast implant-associated anaplastic large cell lymphoma: updated results from a structured expert consultation process	Kim et al [52]	PLASTIC AND RECONSTRUCTIVE SURGERY-GLOBAL OPEN	32	2015	Rand Health, Boston	USA
45	Breast implant related anaplastic large cell lymphoma presenting as late onset pen-implant effusion	Smith et al [53]	BREAST	32	2012	Ascot Integrated Hospital, Auckland	New Zealand
46	Breast implant-associated anaplastic large cell lymphoma a systematic review	Leberfinger et al [54]	JAMA SURGERY	31	2017	Penn State Health Milton S. Hershey Medical Center, Pennsylvania	USA
47	Breast implant-associated anaplastic large cell lymphoma: report of 2 cases and review of the literature	Hart et al [55]	AESTHETIC SURGERY JOURNAL	30	2014	Winship Cancer Institute , Atlanta	USA
48	Implant-associated primary anaplastic large-cell lymphoma with simultaneous involvement of bilateral breast capsules	Bautista-Quach et al [56]	CLINICAL BREAST CANCER	30	2013	City of Hope National Medical Centre, Duarte	USA
49	Breast implant associated anaplastic large cell lymphoma: the UK experience. Recommendations on its management and implications for informed consent	Johnson et al [57]	EJSO	25	2017	St Bartholomews Hospital, London	UK
50	Anaplastic large cell lymphoma of the breast arising around mammary implant capsule: an Italian report	Farace et al [58]	AESTHETIC PLASTIC SURGERY	20	2013	University of Sassari	ITALY

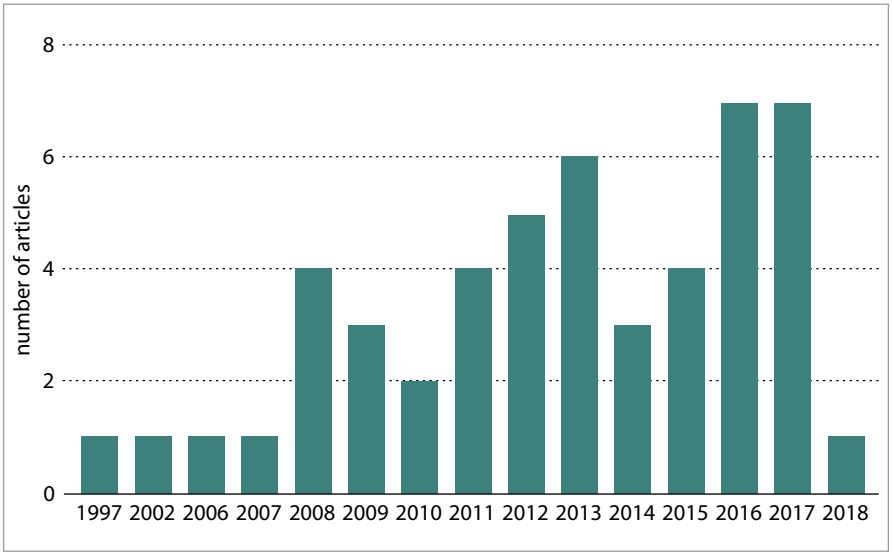
same. As observed in similar studies [6–8], this would allow us to appreciate the evolution of our knowledge and understanding of this disease.

Citation is the acknowledgment received by an article from another, later one. The number of times an article is cited can be a representation of its overall impact [9]. Citation analysis is a tool to study such relations between articles and may be used to identify the most cited studies, which would have the most impact. In this study, we sought to create a compilation of landmark, peer reviewed articles and to classify them according to the topics they focus on. We hope this article proves to be a useful resource for future plastic surgeons and to the industry involved in the manufacture of breast prostheses. Here we report on the 50 most cited articles pertaining to the field of BIA-ALCL.

Methods

Article selection

For the purpose of identifying the high impact articles, we searched the Web



Graph 1. Distribution of published articles across the years.

of Science Citation Index in November 2019. The search included all years until 2019 and all the databases available through Web of Science. Various combinations of key words such as: BIA-ALCL, breast implant-associated anaplastic large cell lymphoma, breast implant non-Hodgkin's lymphoma, breast implant illness, anaplastic lymphoma and breast implant, were used to obtain several search results. All results were compared among each other by individually reviewing the resultant articles and "breast implant-associated anaplastic large cell lymphoma" was selected as the main search term. This initial search returned 325 articles. Following this, articles from the other reports which were focused on the field of BIA-ALCL were included in this study according to the number of citations they received. Subsequently the top 50 articles [1,10–58] (with the highest number of citations) were extracted from this compiled list of articles. Since literature reviews are not original articles, but still have a high citation rate, including them would have skewed the results and so they were excluded.

Data extraction

The articles sourced were subsequently analyzed based on their publishing journal, authorship, publication year, institution and country of origin, type of study (basic science or clinical research), level of evidence (LoE), and study topic. The articles were then classified and categorized according to the same.

Tab. 2. Countries of origin of the articles.

No.	Country	Number of articles	Total number of citations	Average number of citations
1	USA	33	2,167	65.67
2	Australia	7	515	73.57
3	Netherlands	2	259	129.5
4	UK	2	75	37.5
5	Italy	2	54	27
6	France	1	80	80
7	Germany	1	49	49
8	Canada	1	44	44
9	New Zealand	1	32	32

Results

Following collection, the 50 most cited articles were included in this study. Tab. 1 illustrates these publications in the descending order of their number of citations. The earliest article considered for this study was from August 1997 and the latest was from January 2018. The highest number of publications were in 2016 and 2017 with seven articles each. This is highlighted in Graph 1 which shows the distribution of published articles across the years. The United States of America was found to have a significantly higher number of publications (N = 33) compared to the 8 other nations (Tab. 2). On the other hand, in terms of the average number of citations per article, the Netherlands leads by a wide margin. Among the institutes of the origin of these articles, University of Texas, MD Anderson Cancer Center had the highest number of publications (N = 8) followed by Peter MacCallum Cancer Centre and Macquarie University with 3 articles each (Tab. 3).

The collected articles were published across 30 journals. Tab. 4 displays these journals. *Plastic and Reconstructive Surgery* was a journal with the majority of publications (N = 13). Tab. 5 lists the authors with 2 articles among the 50 most cited. Tab. 6 show cases of the top 10 authors according to their total number of citations and among them H. Hu tops the list with 229 citations, followed by R. N. Miranda with 211 citations and D. de Jong with 189 citations. Among the included publications, 8 were basic science studies and the rest were clinical research studies. The articles were further classified based on their level of evidence in Tab. 7 according to the protocols developed by Oxford Centre for

Tab. 3. Institutes of origin of the articles.

No.	Institute	Number of articles
1	Ascot Integrated Hospital, Auckland	1
2	Boston University School of Medicine, Boston	1
3	Brigham and Women's Hospital	1
4	Charité Universitätsmedizin, Berlin	1
5	City of Hope National Medical Centre, Duarte	2
6	Columbia Univ, New York	1
7	Cooper University Hospital	1
8	Dana-Farber Cancer Institute, Boston	1
9	Emory Univ. School of Medicine, Atlanta	1
10	Henderson Hospital, Ontario	1
11	Institut Universitaire du Cancer-Oncopole	1
12	Keck School of Medicine, University of Southern California	1
13	Macquarie University	3
14	Mayo Clinic	1
15	Netherlands Cancer Institute	1
16	Penn State Health Milton S. Hershey Medical Center, Pennsylvania	1
17	Peter MacCallum Cancer Centre	3
18	Rand Health and Pardee Rand Graduate School	1
19	Rand Health, Boston	2
20	Roger Williams Medical Centre, Providence	1
21	Royal Melbourne Hospital, Parkville	1
22	Sapienza University, Sant Andrea Hospital, Rome	1
23	St Bartholomews Hospital, London	1
24	Surgical Aesthetics, London	1
25	Tufts University school of Medicine, Baystate Medical Centre	1
26	University of Florida College of Medicine	1
27	University of Pittsburgh	1
28	University of Sassari	1
29	University of Southern California	3
30	University of Texas MD Anderson Cancer Center	8
31	University of Texas, Southwestern Medical centre	1
32	USC Kerk School of Medicine LA	1
33	Virginia Commonwealth University Medical Centre	1
34	VU University Medical Centre, Amsterdam	1
35	Wi nship Cancer Institute, Atlanta	1

Evidence-Based Medicine [59,60]. Most of the articles in this study had LoE 5 (N = 19) and none were found to have LoE 1.

Discussion

Citation analysis has been performed on the literature of the various subspecialties of plastic surgery such as microsurgery [61,62], hand surgery [63], craniofacial surgery [64–67], breast surgery [7,68], cleft lip surgery [69,70] and lower extremity reconstruction [71], among others. However, to the best of our knowledge, this is the first time it has been carried out on the field of BIA-ALCL. Through this study, we hoped to create a compilation of important publications that have contributed to the evolution and development of this field. Although each article is worthy of discussion, here we briefly comment on the most cited articles and the high impact publications focused on the different areas of interest (pathophysiology, diagnostics, oncologic management, databases, case series and reports).

The article with the highest number of citations (189 citations) authored by D. de Jong in 2008 describes a study to determine the risk of ALCL associated with breast implants. Following the identification of 2 patients with ALK-negative ALCL close to implanted breast prostheses, the authors investigated the national database of Netherlands to identify 11 patients with similar findings. This study postulates three mechanisms of causation for this pathology, and concludes that though the risk is low, there is an association between silicone breast implants and ALCL [10].

Second on our list of highest impact articles is the pioneer report on BIA-ALCL by J. A. Keech a B. Creech, authored in 1997. This article details the follow-up care of a singular patient from November 1991 to 1996, who presented with a peri-implant lesion in late 1995. Prior to this report, there is no literature discussing this disease entity and there was only speculation regarding an association between breast implants and cutaneous lymphoma [1].

With 147 citations, the third article on the list was published in 2014 and was authored by R. N. Miranda from University of Texas MD Anderson Cancer Centre. The authors performed clinical follow up on 60 published cases of breast

Tab. 4. Journals with articles in the top 50.

No.	Journal	Journal impact factor	Number of articles
1	JAMA-JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION	51.3	1
2	AESTHETIC PLASTIC SURGERY	1.399	1
3	AESTHETIC SURGERY JOURNAL	3.48	3
4	AMERICAN JOURNAL OF SURGICAL PATHOLOGY	6.155	2
5	ANNALS OF ONCOLOGY	13.926	1
6	ANNALS OF PLASTIC SURGERY	1.448	1
7	APPLIED IMMUNOHISTOCHEMISTRY & MOLECULAR MORPHOLOGY	1.863	1
8	ARCHIVES OF PATHOLOGY & LABORATORY MEDICINE	4.151	1
9	BREAST	3.494	1
10	BREAST CANCER RESEARCH AND TREATMENT	3.471	1
11	BRITISH JOURNAL OF HAEMATOLOGY	5.206	1
12	CANCER	6.102	1
13	CLINICAL BREAST CANCER	2.762	1
14	CLINICAL CANCER RESEARCH	8.911	1
15	CURRENT HEMATOLOGIC MALIGNANCY REPORTS	2.397	1
16	DIAGNOSTIC PATHOLOGY	2.528	1
17	EJSO	3.379	1
18	HAEMATOLOGICA	7.57	1
19	HAEMATOLOGICA-THE HEMATOLOGY JOURNAL	7.57	1
20	INTERNATIONAL JOURNAL OF CLINICAL AND EXPERIMENTAL PATHOLOGY	1.706	2
21	JAMA ONCOLOGY	22.416	1
22	JAMA SURGERY	10.668	1
23	JOURNAL OF CLINICAL ONCOLOGY	28.245	2
24	JOURNAL OF PLASTIC RECONSTRUCTIVE AND AESTHETIC SURGERY	2.228	2
25	LEUKEMIA & LYMPHOMA	2.674	3
26	MODERN PATHOLOGY	6.365	1
27	ONCOLOGIST	5.252	1
28	PLASTIC AND RECONSTRUCTIVE SURGERY	3.946	13
29	PLASTIC AND RECONSTRUCTIVE SURGERY-GLOBAL OPEN	0.67	1
30	VIRCHOWS ARCHIV	2.585	1

Tab. 5. Authors with 2 articles in top 50.

No.	Author's name
1	Clemens, M.W.
2	Hu, H.
3	Kim, B.
4	Kadin, M.E.
5	Thompson, P.A.
6	Lechner, M.G.
7	Miranda, R.N.

Tab. 6. Top 10 authors.

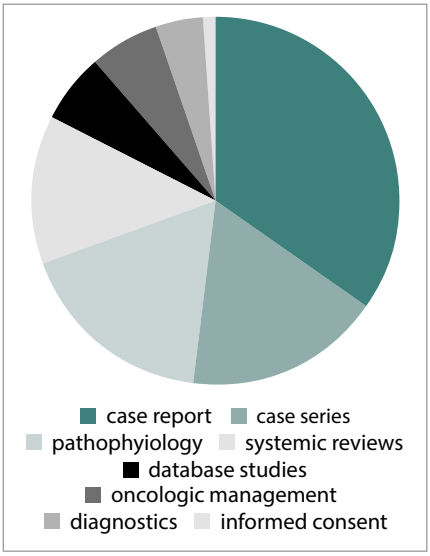
Rank	Author	Total number of citations
1	Hu, H.	229
2	Miranda, R.N.	211
3	de Jong, D.	189
4	Keech, J.A.	161
5	Clemens, M.W	151
6	Kadin, M.E.	142
7	Brody, G.S.	137
7	Kim, B.	137
9	Roden, A.C.	111
10	Lechner, M.G.	102

Tab. 7. Level of evidence of the articles.

Level of evidence	Number of articles
1	0
2	1
3	3
4	11
5	19

implant associated ALCL from 1997 to December 2012. They observed the overall survival as well as the oncological management of these patients. In conclusion, this study states that with capsulectomy and implant removal, most patients achieved complete remission [11].

Moving on to the specific fields of interest, we observed that among the articles describing the pathophysiology of this disease, the study by H. Hu published in 2016 in *Plastic and Reconstructive Surgery* journal has the highest number of citations (127 citations). This



Graph 2. Distribution of topics.

Tab. 8. Top 5 institutes.

No.	Institute	Number of articles
1	University of Texas MD Anderson Cancer Center, USA	8
2	Peter MacCallum Cancer Centre, Melbourne, Australia	3
3	Macquarie University, Australia	3
4	City of Hope National Medical Centre, Duarte, USA	2
5	Rand Health, Boston, USA	2

Tab. 9. Top 5 journals.

No.	Journals	Number of articles
1	PLASTIC AND RECONSTRUCTIVE SURGERY	13
2	AESTHETIC SURGERY JOURNAL	3
3	LEUKEMIA & LYMPHOMA	3
4	AMERICAN JOURNAL OF SURGICAL PATHOLOGY	2
5	INTERNATIONAL JOURNAL OF CLINICAL AND EXPERIMENTAL PATHOLOGY	2

article describes the discovery of a distinct microbiome and bacterial biofilm in histological samples from BIA-ALCL patients suggesting a possible role of infection as a causative agent. This article also suggests that strategies to reduce implant contamination must be adopted as well as improved [12].

In the field of diagnostics, the publication with the most citations was received by M. E. Kadin from Boston University School of Medicine. Published in *Aesthetic Surgery Journal* in 2016, this article received 71 citations. In this study the authors suggest certain biomarkers like JunB and SATB1 as possible indicators to identify the risk of developing BIA-ALCL [13].

Among the studies focused on the oncological management of BIA-ALCL, the aforementioned article by Miranda et al tops the list. This is followed by "Complete surgical excision is essential for the management of patients with breast implant-associated anaplastic large cell lymphoma" , an article authored by M. W. Clemens in 2016 which received 117 citations. The authors performed a clinical follow up of 87 patients, and reported on their overall survival. Also they compared the outcomes of different management strategies such as partial and total capsulectomy, systemic chemotherapy, radiation therapy and concluded that complete surgical excision achieves the best outcomes [14].

Excluding the pioneering report by Keech et al, the case report with the highest number of citations was by A. C. Roden from Mayo Clinic, Rochester, Minnesota (111 citations). In this study from 2008, the authors followed the progress of therapy of 4 patients diagnosed with primary ALCL adjacent to breast prostheses and was able to showcase the indolent nature of this disease entity [15]. Among systemic reviews, the most influential one received 137 citations and was authored by G. S. Brody in 2015. In this article, the authors performed a review of the existing literature at the time and also reported on a number of new cases [16].

The mean number of citations of these 50 most cited articles was calculated to be 65.5 citations. The authors observed (Graph 2) that the majority of the high impact literature on BIA-ALCL are case reports (36%; N = 18) followed by case series (18%; N = 9) and articles on its pathophysiology (16%; N = 8). There were 3 articles focusing on the topic of oncologic management, 2 on diagnostics and 1 on informed consent. The rest of the publications were systemic reviews (12%; N = 6) and database studies (6%; N = 3). This showcases that the lion's share of the existing literature on BIA-ALCL is focused on the monitoring of this disease entity. Therefore, there may be a need for future studies to investigate the fields of diagnosis and oncological management.

Regarding their origin, the nation with the highest number of articles was the USA (66%; N = 33); whereas among the institutes, University of Texas MD Anderson Cancer Center tops the list (Tab. 8). The high volume of research originating in the USA may be attributed partly to the large number of breast reconstruction procedures being performed there [72,73]. Most of the articles were published in *Plastic and Surgery Journal* (26%; N = 13). The second place was shared by *Aesthetic Surgery Journal and Leuke-*

mia and Lymphoma with 3 articles each (Tab. 9). The majority of the included studies had LoE 5 (38%; N = 19), while only one article achieved LoE 2. The lack of articles with LoE 1, i.e. randomized controlled trials, may be partly attributed to the unique challenges faced in generating such evidence [74–76].

The Web of Science Citation Index was the only tool used for our data collection and therefore this study is limited by its accuracy. Another limitation is that though citation analysis was used here to stratify the articles, it is not necessarily a measure of the scientific quality or influence of the individual manuscripts. A further shortcoming of this study was that only articles in the English language were taken into consideration. Though the number of citations may represent the impact of an article on the literature, it can be influenced by many external factors and bias [77].

Conclusion

To the best of our knowledge this is the first time citation analysis has been performed on publications pertaining to BIA-ALCL. Through this study we see that the majority of existing literature is focused on the monitoring of this disease entity. Thus, there may be a need to further investigate the pathophysiology and to develop strategies for diagnosis, and protocols for oncological management.

Roles of authors: The first author, Austin Paul Kallarackal was involved in writing the manuscript and the collection of articles via Web of Science citation index, and also partly worked on the extraction and compilation of the data. Igor Slaninka provided the guidance and support to come up with the research question, decide on the correct search terms and finalize the articles to be included. Nancy Mrozková was involved in working on the collected articles, compiling them into the final list of articles and also in extracting the required data.

Disclosure: The authors declared no potential conflicts of interest with respect to the research, authorship and publication of this article.

Funding: The authors received no financial support for the research, authorship and publication of this article.

References

1. Keech JA. Jr, Creech BJ. Anaplastic T-cell lymphoma in proximity to a saline-filled breast implant. *Plast Reconstr Surg.* 1997, 100(2): 554–555.
2. Rastogi P., Riordan E., Moon D., et al. Theories of etiopathogenesis of breast implant-associated anaplastic large cell lymphoma. *Plast Reconstr Surg.* 2019, 143 (3S): 23S–29S.
3. Swerdlow SH., Campo E., Pileri SA., et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood* 2016, 127(20): 2375–2390.
4. Di Napoli A. Achieving Reliable Diagnosis in Late Breast Implant Seromas: From Reactive to Anaplastic Large Cell Lymphoma. *Plast Reconstr Surg*. 2019, 143(3S): 15S–22S.
5. Collett DJ., Rakhorst H., Lennox P., et al. Current risk estimate of breast implant-associated anaplastic large cell lymphoma in textured breast implants. *Plast Reconstr Surg*. 2019, 143 (3S): 30S–40S.
6. Kreutz-Rodrigues L., Shapiro D., Mardini S., et al. Landmarks in facial rejuvenation surgery: the top 50 most cited articles. *Aesthet Surg J*. 2020, 40(1): NP1–NP7.
7. Uysal E. Top 100 cited classic articles in breast cancer research. *Eur J Breast Health*. 2017, 13(3): 129–137.
8. Joyce KM., Joyce CW., Kelly JC., et al. Levels of evidence in the plastic surgery literature: a citation analysis of the top 50 "classic" papers. *Arch Plast Surg*. 2015, 42(4): 411–418.
9. Paladugu R., Schein M., Gardezi S., et al. One hundred citation classics in general surgical journals. *World J Surg*. 2002, 26(9): 1099–1105.
10. de Jong D., Vasmel WLE., de Boer JP., et al. Anaplastic large-cell lymphoma in women with breast implants. *JAMA*. 2008, 300(17): 2030–2035.
11. Miranda RN., Aladily TN., Prince HM., et al. Breast implant-associated anaplastic large-cell lymphoma: long-term follow-up of 60 patients. *J Clin Oncol*. 2014, 32(2): 114–120.
12. Hu H., Johani K., Almatroudi A., et al. Bacterial biofilm infection detected in breast implant--associated anaplastic large-cell lymphoma. *Plast Reconstr Surg*. 2016, 137(6): 1659–1669.
13. Kadin ME., Deva A., Xu H., et al. Biomarkers provide clues to early events in the pathogenesis of breast implant-associated anaplastic large cell lymphoma. *Aesthet Surg J*. 2016, 36(7): 773–781.
14. Clemens MW., Medeiros LJ., Butler CE., et al. Complete surgical excision is essential for the management of patients with breast implant--associated anaplastic large-cell lymphoma. *J Clin Oncol*. 2016, 34(2): 160–168.
15. Roden AC., Macon WR., Keeney GL., et al. Seroma-associated primary anaplastic large-cell lymphoma adjacent to breast implants: an indolent T-cell lymphoproliferative disorder. *Mod Pathol*. 2008, 21(4): 455–463.
16. Brody GS., Deapen D., Taylor CR., et al. Anaplastic large cell lymphoma occurring in women with breast implants: analysis of 173 cases. *Plast Reconstr Surg*. 2015, 135(3): 695–705.
17. Kim B., Roth C., Chung KC., et al. Anaplastic large cell lymphoma and breast implants: a systematic review. *Plast Reconstr Surg*. 2011, 127(6): 2141–2150.
18. Hu H., Jacombs A., Vickery K., et al. Chronic biofilm infection in breast implants is associated with an increased T-cell lymphocytic infiltrate: implications for breast implant-associated lymphoma. *Plast Reconstr Surg*. 2015, 135(2): 319–329.
19. Loch-Wilkinson A., Beath KJ., Knight RJW., et al. breast implant-associated anaplastic large cell lymphoma in Australia and New Zealand: high-surface-area textured implants are associated with increased risk. *Plast Reconstr Surg*. 2017, 140(4): 645–654.
20. Aladily TN., Medeiros LJ., Amin MB., et al. Anaplastic large cell lymphoma associated with breast implants: a report of 13 cases. *Am J Surg Pathol*. 2012, 36(7): 1000–1008.
21. Doren EL., Miranda RN., Selber JC., et al. U.S. epidemiology of breast implant-associated anaplastic large cell lymphoma. *Plast Reconstr Surg.* 2017, 139(5): 1042–1050.
22. Laurent C., Delas A., Gaulard P., et al. Breast implant-associated anaplastic large cell lymphoma: two distinct clinicopathological variants with different outcomes. *Ann Oncol.* 2016, 27(2): 306–314.
23. Kadin ME., Morgan J., Xu H., et al. CD30+ T cells in late seroma may not be diagnostic of breast implant-associated anaplastic large cell lymphoma. *Aesthet Surg J.* 2017, 37(7): 771–775.
24. de Boer M., van Leeuwen FE., Hauptmann M., et al. Breast implants and the risk of anaplastic large-cell lymphoma in the breast. *JAMA Oncol*. 2018, 4(3): 335–341.
25. Gaudet G., Friedberg JW., Weng A., et al. Breast lymphoma associated with breast implants: two case-reports and a review of the literature. *Leuk Lymphoma*. 2002, 43(1): 115–119.
26. Miranda RN., Lin L., Talwalkar SS., et al. Anaplastic large cell lymphoma involving the breast: a clinicopathologic study of 6 cases and review of the literature. *Arch Pathol Lab Med*. 2009, 133(9): 1383–1390.
27. Carty MJ., Pribaz JJ., Antin JH., et al. A patient death attributable to implant-related primary anaplastic large cell lymphoma of the breast. *Plast Reconstr Surg*. 2011, 128(3):112e–118e.
28. Newman MK., Zemmel NJ., Bandak AZ., et al. Primary breast lymphoma in a patient with silicone breast implants: a case report and review of the literature. *J Plast Reconstr Aesthet Surg*. 2008, 61(7): 822–825.
29. Thompson PA., Lade S., Webster H., et al. Effusion-associated anaplastic large cell lymphoma of the breast: time for it to be defined as

a distinct clinico-pathological entity. *Haematologica*. 2010, 95(11): 1977–1979.
30. Wong AK., Lopategui J., Clancy S., et al. Anaplastic large cell lymphoma associated with a breast implant capsule: a case report and review of the literature. *Am J Surg Pathol*. 2008, 32(8): 1265–1268.
31. Lechner MG., Megiel C., Church CH., et al. Survival signals and targets for therapy in breast implant-associated ALK – anaplastic large cell lymphoma. *Clin Cancer Res*. 2012, 18(17): 4549–4559.
32. Berry MG., Stanek JJ. The PIP mammary prosthesis: a product recall study. *J Plast Reconstr Aesthet Surg*. 2012, 65(6): 697–704.
33. Fritzsche FR., Pahl S., Petersen I., et al. Anaplastic large-cell non-Hodgkin's lymphoma of the breast in periprosthetic localisation 32 years after treatment for primary breast cancer – a case report. *Virchows Arch*. 2006, 449(5): 561–564.
34. Lechner MG., Lade S., Liebertz DJ., et al. Breast implant-associated, alk-negative, t-cell, anaplastic, large-cell lymphoma: establishment and characterization of a model cell line (TLBR-1) for this newly emerging clinical entity. *Cancer*. 2011, 117(7): 1478–1489.
35. Li S., Lee AK. Silicone implant and primary breast ALK1-negative anaplastic large cell lymphoma, fact or fiction? *Int J Clin Exp Pathol*. 2010, 3(1): 117–127.
36. Srinivasa DR., Miranda RN., Kaura A., et al. Global adverse event reports of breast implant-associated alcl: an international review of 40 government authority databases. *Plast Reconstr Surg*. 2017, 139(5): 1029–1039.
37. Gidengil CA., Predmore Z., Mattke S., et al. Breast implant-associated anaplastic large cell lymphoma: a systematic review. *Plast Reconstr Surg*. 2015, 135(3): 713–720.
38. Taylor CR., Siddiqi IN., Brody GS., et al. Anaplastic large cell lymphoma occurring in association with breast implants: review of pathologic and immunohistochemical features in 103 cases. *Appl Immunohistochem Mol Morphol.* 2013, 21(1): 13–20.
39. Popplewell L., Thomas SH., Huang Q., et al. Primary anaplastic large-cell lymphoma associated with breast implants. *Leuk Lymphom*a. 2011, 52(8): 1481–1487.
40. Olack B., Gupta R., Brooks GS. Anaplastic large cell lymphoma arising in a saline breast implant capsule after tissue expander breast reconstruction. *Ann Plast Surg*. 2007, 59(1): 56–57.
41. Alobeid B., Sevilla DW., El-Tamer MB., et al. Aggressive presentation of breast implant-associated ALK-1 negative anaplastic large cell lymphoma with bilateral axillary lymph node involvement. *Leuk Lymphoma*. 2009, 50(5): 831–833.
42. Blombery P., Thompson ER., Jones K., et al. Whole exome sequencing reveals activating JAK1 and STAT3 mutations in breast implant-associated anaplastic large cell lymphoma anaplastic large cell lymphoma. *Haematologica.* 2016, 101(9): e387–e390.
43. Taylor KO., Webster HR., Prince HM. Anaplastic large cell lymphoma and breast implants: five Australian cases. *Plast Reconstr Surg*. 2012, 129(4): 610e–617e.
44. Adrada BA., Miranda RN., Rauch GM., et al. Breast implant-associated anaplastic large cell lymphoma: sensitivity, specificity, and findings of imaging studies in 44 patients. *Breast Cancer Res Treat*. 2014, 147(1): 1–14.
45. Bishara MRY., Ross C., Sur M.. Primary anaplastic large cell lymphoma of the breast arising in reconstruction mammoplasty capsule of saline filled breast implant after radical mastectomy for breast cancer: an unusual case presentation. *Diagn Pathol*. 2009, 4: 11.
46. George EV., Pharm J., Houston C., et al. Breast implant-associated ALK-negative anaplastic large cell lymphoma: a case report and discussion of possible pathogenesis. *Int J Clin Exp Pathol*. 2013, 6(8): 1631–1642.
47. Adams WP. Jr, Culbertson EJ., Deva AK., et al. Macrotextured breast implants with defined steps to minimize bacterial contamination around the device: experience in 42,000 implants. *Plast Reconstr Surg*. 2017, 140(3): 427–431.
48. Thompson PA., Prince HM. Breast implant-associated anaplastic large cell lymphoma: a systematic review of the literature and mini-meta analysis. *Curr Hematol Malig Rep*. 2013, 8(3): 196–210.
49. Story SK., Schowalter MK., Geskin LJ. Breast implant-associated ALCL: a unique entity in the spectrum of CD30+ lymphoproliferative disorders. *Oncologist*. 2013, 18(3): 301–307.
50. Di Napoli A., Jain P., Duranti E., et al. Targeted next generation sequencing of breast implant-associated anaplastic large cell lymphoma reveals mutations in JAK/STAT signalling pathway genes, TP53 and DNMT3A. *Br J Haematol.* 2018, 180(5): 741–744.
51. Roden MW., Miranda RN., Butler CE. Breast implant informed consent should include the risk of anaplastic large cell lymphoma. *Plast Reconstr Surg*. 2016, 137(4): 1117–1122.
52. Kim B., Predmore ZS., Mattke S., et al. Breast implant-associated anaplastic large cell lymphoma: updated results from a structured expert consultation process. *Plast Reconstr Surg Glob Open*. 2015, 3(1): e296.
53. Smith TJ., Ramsaroop R. Breast implant related anaplastic large cell lymphoma presenting as late onset peri-implant effusion. *Breast*. 2012, 21(1): 102–104.
54. Leberfinger AN., Behar BJ., Williams NC., et al. Breast implant-associated anaplastic large cell lymphoma: a systematic review. *JAMA Surg.* 2017, 152(12): 1161–1168.
55. Hart AM., Lechowicz MJ., Peters KK., et al. Breast implant-associated anaplastic large cell lymphoma: report of 2 cases and review of the literature. *Aesthet Surg J*. 2014, 34(6): 884–894.
56. Bautista-Quach MA., Nademanee A., Weisenburger DD., et al. Implant-associated primary anaplastic large-cell lymphoma with simultaneous involvement of bilateral breast capsules. *Clin Breast Cancer*. 2013, 13(6): 492–495.
57. Johnson L., O'Donoghue JM., McLean N., et al. Breast implant associated anaplastic large cell lymphoma: The UK experience. Recommendations on its management and implications for informed consent. *Eur J Surg Oncol.* 2017, 43(8): 1393–1401.
58. Farace F., Bulla A., Marongiu F., et al. Anaplastic large cell lymphoma of the breast arising around mammary implant capsule: an Italian report. *Aesthetic Plast Surg*. 2013, 37(3): 567–571.
59. Oxford Centre for Evidence-Based Medicine Levels of Evidence. [online]. Available from: https://www.cebm.net/2016/05/ocebm-levels-of-evidence/.
60. Sinha Y., Iqbal FM., Spence JN., et al. A bibliometric analysis of the 100 most-cited articles in rhinoplasty. *Plast Reconstr Surg Glob Open.* 2016, 4(7): e820.
61. Kim K., Ibrahim AM., Koolen PG., et al. Highest impact articles in microsurgery: a citation analysis. *J Reconstr Microsurg*. 2015, 31(7): 527–540.
62. Joyce CW., Carroll SM. Microsurgery: the top 50 classic papers in plastic surgery: a citation analysis. *Arch Plast Surg*. 2014, 41(2): 153–157.
63. Joyce CW., Kelly JC., Carroll SM. The 100 top-cited classic papers in hand surgery. *J Plast Surg Hand Surg*. 2014, 48(4): 227–233.
64. Mahon NA., Joyce CW., Thomas S., et al. The 50 most cited papers in craniofacial anomalies and craniofacial surgery. *Arch Plast Surg*. 2015, 42(5): 559–566.
65. Whitney E., Mahato D., Odell T., et al. The 100-most cited articles about craniectomy and hemicraniectomy: a bibliometric analysis. *Cureus.* 2019, 11(8): e5524.
66. Tahiri Y., Fleming TM., Greathouse T., et al. Analysis of the 50 most cited papers in craniofacial surgery. *J Craniomaxillofac Surg*. 2015, 43(10): 2152–2157.
67. Chang MT., Schwam ZG., Schutt CA., et al. The 50 most cited articles in facial plastic surgery. *Aesthetic Plast Surg*. 2017, 41(5): 1202–1207.
68. Muslu Ü. The evolution of breast reduction publications: a bibliometric analysis. *Aesthetic Plast Surg*. 2018, 42(3): 679–691.
69. Christou P., Antonarakis GS. The 100 most-cited human cleft lip and palate-related articles published in dentistry, oral surgery, and medicine journals. *Cleft Palate Craniofac J*. 2015, 52(4): 437–446.
70. Mahon NA., Joyce CW. A bibliometric analysis of the 50 most cited papers in cleft lip and palate. *J Plast Surg Hand Surg*. 2015, 49(1): 52–58.

71. Mbaidjol Z., Rothenberger J., Chetany R. A scientometric analysis of the 50 most cited articles for reconstruction of the lower extremity. *Surg Res Pract*. 2019, 2019: 3068028.
72. Wilkins EG., Alderman AK. Breast reconstruction practices in North America: current trends and future priorities. *Semin Plast Surg*. 2004, 18(2): 149–155.
73. Moghimi M., Fathi M., Marashi A., et al. A scientometric analysis of 20 years of research on breast reconstruction surgery: a guide for research design and journal selection. *Arch Plast Surg*. 2013, 40(2): 109–115.
74. Joyce CW., Joyce KM., Sugrue CM., et al. Plastic surgery and the breast: a citation analysis of the literature. *Plast Reconstr Surg Glob Open*. 2(11): e251.
75. Solomon MJ., Laxamana A., Devore L., et al. Randomized controlled trials in surgery. *Surgery*. 1994, 115(6): 707–712.
76. van der Linden W. Pitfalls in randomized surgical trials. Surgery. 1980, 87(3): 258–262.
77. Asaad M., Kallarackal AP., Meaike J., et al. Citation skew in plastic surgery journals: does the journal impact factor predict individual article citation rate? *Aesthet Surg J*. 2020, 40(10): 1136–1142.

Austin Paul Kallarackal, MD
Faculty of Medicine in Hradec Kralove,
Charles University in Prague
Šimkova 870
500 03 Hradec Králové
Czech Republic
e-mail: austinpaul@gmail.com

Submitted: 27.3.2021
Accepted: 28.7.2021

doi: 10.48095/ccachp2021139

Bone invasion by oral squamous cell carcinoma

D. Král[1], R. Pink[1], L. Šašková[1], J. Michálek[2], P. Tvrdý[1]

[1] Department of Oral and Maxillofacial Surgery, Faculty of Medicine and Dentistry, Palacký University Olomouc and University Hospital Olomouc, Czech Republic

[2] Department of Clinical and Molecular Pathology, Faculty of Medicine and Dentistry, Palacký University Olomouc and University Hospital Olomouc, Czech Republic

Summary

Background: With regards to the anatomical relationships in the mouth, oral squamous cell carcinoma can invade the maxilla or the mandible. According to the TNM system, tumours that invade through cortical bone are classified as T4a, stage IVA. Bone invasion by oral squamous cell carcinoma most often occurs in tumours close to the bone or in larger and more advanced tumours. It is considered an adverse prognostic factor and it is often a diagnostic and therapeutic problem. Destruction of the bone tissue is mediated by activated osteoclasts rather than directly by carcinoma. Tumor necrosis factors – receptor activator of NF-kB (RANK), receptor activator of NF-kB ligand (RANKL) and osteoprotegerin (OPG) – play an important role in osteoclastogenesis. According to histological point of view, there are three patterns of bone invasion – erosive, mixed and infiltrative. The most commonly used imaging techniques when evaluating bone invasion by oral squamous cell carcinoma include CT and MRI. **Purpose:** This review is focused on the cellular and molecular mechanisms, histological patterns and detection methods of bone invasion caused by oral squamous cell carcinoma.

Key words

oral squamous cell carcinoma – bone invasion – osteoclast

Král D., Pink R., Šašková L., et al. Bone invasion by oral squamous cell carcinoma. Acta Chir Plast. 2021, 63(3): 139–144.

Introduciton

Approximately 30% of all head and neck cancers are malignant tumours of the oral cavity. Histologically, more than 90% of these are squamous cell carcinomas [1]. According to global statistics, where oral squamous cell carcinoma (OSCC) is presented together with oropharyngeal carcinoma, it is the 6th most common cancer in the world. About 300,000 of new OSCC cases are diagnosed every year and aproximately two thirds of these cases are diagnosed in developing countries from areas such as South and Southeast Asia, Eastern Europe and parts of Latin America [2]. At least 95% of OSCC cases occur in patients over 40 years of age and OSCC occurs twice as often in men as in women [3]. The main risk factors include smoking, alcohol abuse and betel chewing [4]. Heavy smokers and alcohol drinkers are up to 38-times more at risk of getting the tumour as opposed to abstainers from both products [2]. The human papillomavirus (HPV) plays an important role in oropharyngeal carcinoma. In the case of OSCC, the role of HPV is less important. Oral carcinomas, associated with HPV, occur in about 4% of the cases [5]. Approximately one third of the patients with OSCC are diagnosed in stages I and II. The five-year survival rate is 80% in stage I and 65% in stage II. Unfortunately, the majority of OSCC is diagnosed in advanced stages of the disease (III and IV), where the five-year survival rate is less than 50% and the overall survival rate is 30%, especially because local recurrence or distant metastases often occur [2,6,7].

Bone invasion as a prognostic factor

According to the close anatomical relationships in the oral cavity, carcinomas in the retromolar trigone, gingiva, hard palate, floor of the mouth, buccal mucosa or tongue may involve bone of the maxilla and/or the mandible [8]. The prevalence of jaw bone involvement by OSCC ranges from 5% to 56% [8,9]. The size and the location of the tumour are important in this point of view. It seems that larger or more deeply invading tumours in the soft tissue are more likely to invade the bone. Brown et al [10] showed that 48% of tumours with a diameter of < 4 cm do not invade the bone and 80% of tumours with a diameter of > 4 cm invade the bone. Pandey et al [11] described that the possibility of mandibular involvement is higher in patients where tumors are located within the distance of 1 cm from the mandible. In most cases, tumours enter the bone at the point of abutment rather than preferential entry through the occlusal

surface, neural foramen, or the periodontal membrane [10]. Frequently, this area is in the dentate and edentulous jaws at the junction of the attached and reflected mucosa [10,12,13]. According to Huntley et al [14] in tumours localized lingual to the mandible the site of entry of the tumour into the bone was usually through the alveolar crest with additional spread through the lingual cortex.

According to the TNM system, tumours that invade through cortical bone are classified as T4a, stage IVA. Although many authors consider bone invasion as an independent prognostic factor, there are studies in the literature that point out the prognostic limits of TNM classification in small (≤ 4 cm) OSCC invading the bone [15–17]. Ebrahimi et al [15] suggested modifying the T stage such that the tumours are classified as T1–T3 based on their size and then upstaged by one T stage in the presence of medullary bone invasion. Okura et al [17] recommended the same modification of the TNM classification; however, only for lower gingival OSCC. The results of Kuk et al [16] showed that in small primary OSCC (≤ 4 cm) bone invasion was not significantly associated with disease progression. However, their study pointed out a small subgroup of patients with small OSCC (2–4 cm) with both buccal and lingual bone invasion, which showed a statistically significant worse prognosis compared to the other group of patients with OSCC with or without bone invasion [16]. According to Mücke et al [18] and Petrovic et al [19] in cases of adequate resection margins, the prognosis in patients with bone invasion was not worse. Nevertheless, it has to be taken into account that many studies evaluating bone invasion as a prognostic factor focus only on mandibular invasion. However, OSCC can invade also the maxilla or palatine bone. In this regard, further research is necessary in the future.

The cellular and molecular mechanism of bone invasion

Numerous studies have shown that the destruction of bone associated with the invasion of carcinoma is mediated by osteoclasts rather than directly by malignant cells of the tumor [20–23]. Quan et al [8] described bone invasion as a highly coordinated process, spatially and temporally regulated, in which the following three phases may be distinguished: initial, resorptive and final phase. Various molecules that have different roles in individual phases are involved in the whole process. In the initial phase of bone invasion, when osteoclasts have not yet been recruited, proteases such as matrix metalloproteinases and cathepsins are involved. In the resorptive phase, when osteoclasts play the main role in resorption, cytokines of the tumor necrosis factor (TNF) family and parathyroid hormone-related peptide (PTHrP) are involved. In the final phase, there are growth factors such as epidermal growth factor, transforming growth factor and connective tissue growth factor, which are released from the reservoir within mineralized bone matrix after the destruction. These growth factors promote the growth of neoplastic cells themselves, leading to a vicious cycle that accelerate the process of bone invasion [8,24].

The interaction between osteoblasts, bone marrow stromal cells and osteoclasts is essential in bone remodelling. The balance between them is tightly regulated by many parameters such as mechanical stimulation, hormones and cytokines. Any disturbance between these effectors leads to the development of skeletal abnormalities, characterized by a decrease or an increase in bone mass [25]. It has been proposed that osteoblasts or bone marrow stromal cells are involved in the osteoclastogenesis process via the mechanism involving cell-to-cell contact with osteoclast precursors [3]. The discovery of three proteins from the TNF family that are crucial for the development and activation of osteoclasts is seen as an important finding over the past two decades in bone biology, which supports this hypothesis. Those proteins are the receptor activator of nuclear factor kappa B (RANK), its ligand (RANKL) and osteoprotegerin (OPG) [25,26]. RANKL occurs in two forms – a transmembrane form expressed by osteoblasts, stromal cells and T-lymphocytes, and a soluble form produced by activated T-lymphocytes. Furthermore, RANKL is expressed in lymph nodes, thymus, mammary tissue, lungs and many other tissues. RANK is a transmembrane protein, which is expressed by osteoclasts precursors, mature osteoclasts, dendritic cells as well as some tumour cells, e.g. in breast and prostate carcinoma. OPG is secreted by osteoblasts, stromal cells and a number of other cells in the heart, kidneys, liver and spleen [26]. Soluble and transmembrane forms of RANKL expressed by osteoblasts exert activity through binding to their RANK receptor on osteoclasts [25]. The interaction between RANKL and RANK activates the intercellular signaling cascade, which leads to the differentiation of osteoclast precursors to the osteoclasts called osteoclastogenesis, to bone resorption and the survival of osteoclasts. The OPG acts as a soluble receptor antagonist for RANKL, preventing the binding to the RANK, thereby preventing its activation [27]. Thus, OPG represents a bone protecting molecule [25]. It is believed that the balance of RANKL and OPG expression in osteoblasts and stromal cells is critical for regulating osteoclast differentiation and the function under physiological and pathological conditions [21].

Bone resorption by osteoclast is an important step in the process of bone invasion, progression and metastasis in several malignancies, such as breast cancer, prostate cancer, lung carcinoma, colorectal carcinoma, multiple myeloma and OSCC [20,21,27]. Sato et al [22] showed that RANKL produced by osteoblasts,

stromal cells and carcinoma cells is involved in osteoclastic bone resorption during bone destruction in OSCC. This is also in line with the results of Zhang et al [23] who described that OSCC cells express different levels of both forms of RANKL, transmembrane and soluble and that RANKL directly supports the osteoclastic loss of bone. Tada et al [21] showed that OSCC induced by the suppressed expression of OPG in osteoblasts is involved in osteoclastogenesis. According to another study by Tada et al [20], the differentiation and regulation of osteoclast function is attributed to the modulation of the ratio of RANKL vs. OPG expression by the microenvironment of the tumor and bone, rather than just RANKL expression by OSCC cells. The results of Russmueller et al [27] showed a significantly higher expression of the OPG by OSCC cells in patients with bone invasion compared to patients without bone invasion. Ishikuro et al [28] described that osteoclastic resorption of bone during the invasion of a tumour does not require direct contact of the tumour cells with the osteoclasts of the adjacent bone. He thereby pointed out the significant role of fibrous stroma between the tumour cells and the resorbing bone in bone invasion through RANKL dependent pathway [28]. Despite the significance of the OSCC cells during the osteoclastogenesis, the role of its effects on the function of the osteoclasts is not completely clear. Most of the authors concur that further research is needed in this regard.

Histological patterns of bone invasion

Once the tumour affects the bone, there are three histological patterns of bone invasion: erosive, mixed and infiltrative [12,29,30]. The histological image of an erosive pattern of bone invasion (Fig. 1) is characterized by a broad, expansive tumor front with a sharp interface between the tumour and the bone. It is further characterized by osteoclastic bone resorption and fibrosis along the front of the tumour and the absence of bone islands within the tumour mass. The infiltrative pattern of bone invasion (Fig. 2) is composed of nests of tumor cells with fingerlike projections along an irregular tumour front. There are also residual bone islands within the tumour mass and haversian system penetration. Cases exhibiting features of both patterns, are designated as a mixed pattern [1,3]. Brown et al [10,13] showed that the size and width of the tumor increase the risk of bone invasion and also that the growing size of the tumour and the depth of the invasion into the soft tissue increase the chance of the infiltrative pattern of bone invasion. Thus, the autor assumes

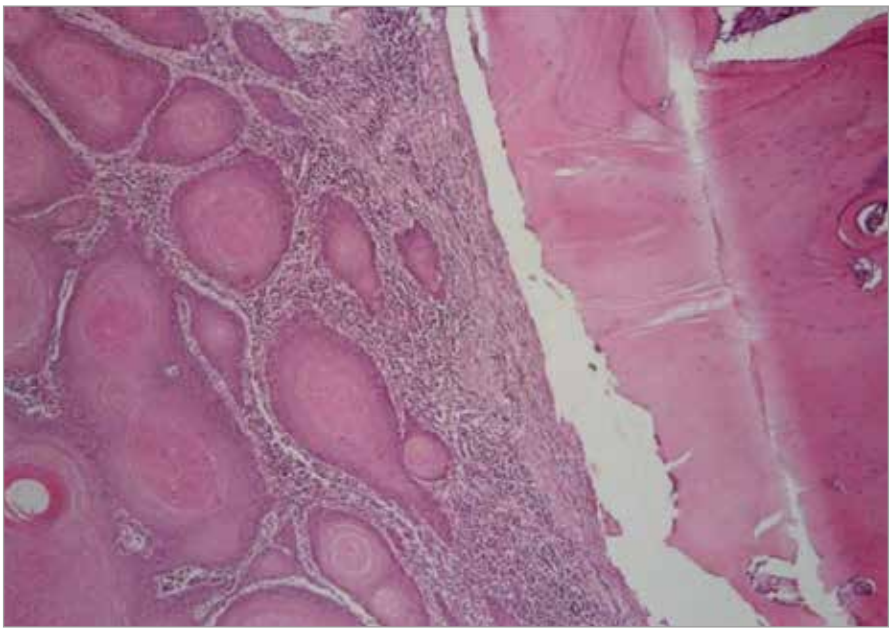


Fig. 1. Erosive pattern of bone invasion by oral squamous cell carcinoma (hematoxylin plus eosin, magnification 40×).

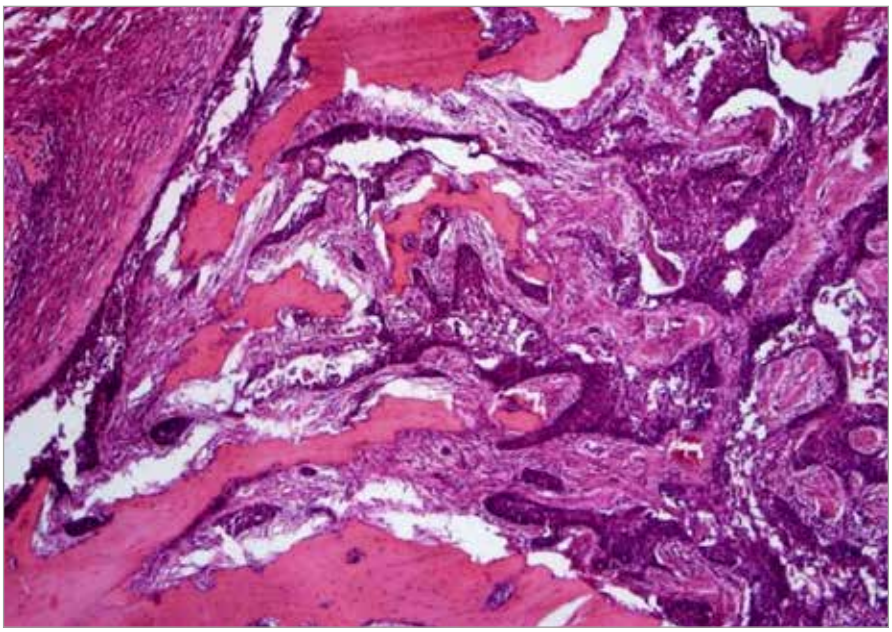


Fig. 2. Infiltrative pattern of bone invasion by oral squamous cell carcinoma (hematoxylin plus eosin, magnification 40×).

that the progression of the tumour into the bone develops the pattern of bone invasion from erosive to mixed and infiltrative. Ishikuro et al [28] also supposes that the erosive and infiltrative pattern of bone invasion represents different stages of the tumour development. Brown et al [10] further stated that neither the pattern of bone invasion nor the fact of whether or not the jaws were dentate or edentolous are not related to the localization of the invasion of the tumour into the bone. Wong et al [1] studied whether the infiltrative pattern of bone invasion is related to a worse prognosis in comparison to the erosive pattern. In their work a three-year disease-free survival in the infiltrative pattern was 30% and 73% in the erosive pattern. They also describe that the infiltrative pattern of bone invasion shows more aggressive behaviour with a higher probability of positive resection margins at tumour excisions and a higher probability of the disease recurrence [1]. Ishikuro et al [28] also agree with this conclusion. In their study, they also showed that the infiltrative pattern of bone invasion shows a higher number of osteoclasts on the surface of the resorpting bone lining the tumour in comparison with the erosive pattern [28]. The possibility of determining the pattern of invasion by intraoperative frozen section is a question of clinical importance. Due to the disruption of the bone's architecture and the difficulty of preparation of frozen section of the bone, this determination is not possible. However, postoperative determination of pattern of bone invasion provides important prognostic information. Therefore this information should be noted on every bone specimen with squamous cell invasion [1].

Detecion of bone invasion

Since the majority of tumours in the oral cavity are visible to the naked eye, the first step in examination of a patient suspected of suffering from OSCC is inspection and palpation. A final diagnosis is based on a histological examination of sample taken by biopsy. However, the correct disease diagnosis and tumor staging, which affect treatment planning, requires the use of complementary imaging techniques capable of offering additional information [31]. The preoperative detection of the presence of bone invasion affecting the facial skeleton in patients with OSCC is critical for planning of surgery and postoperative treatment. According to Zupi et al [32] a clinical examination in evaluating the presence of bone invasion is highly sensitive (82.6%) and is thereby considered to be an essential process. However, for low specificity (44%), a clinical examination is only the first step in further examination. When evaluating the bone invasion, it is possible to use various imaging techniques such as X-ray (Fig. 3) or more reliable techniques such as CT (Fig. 4), MRI or PET/CT. However, every technique has its limitations. According to Rao et al [33] a routine X-ray, including orthopantomogram, are not able to capture the initial bone invasion until 30% of bone minerals are lost. This finding explains the false negative results in evaluating bone invasion of carcinomas using X-rays. Moreover evaluating the area of the mandibular symphysis in orthopantomogram is difficult for summation of the anatomical structures. The most commonly used imaging techniques for examining patients with OSCC include CT and MRI. In terms of limitations of the individual techniques, CT is associated with a higher number of artefacts caused by metal dental materials, while MRI may be burdened with low image quality due to movements of the tongue and swallowing [34]. Many studies deal with the diagnostic accuracy of these imaging tech-

Fig. 3. Orthopantomogram of the patient with squamous cell carcinoma of the left retromolar region of the mandible.

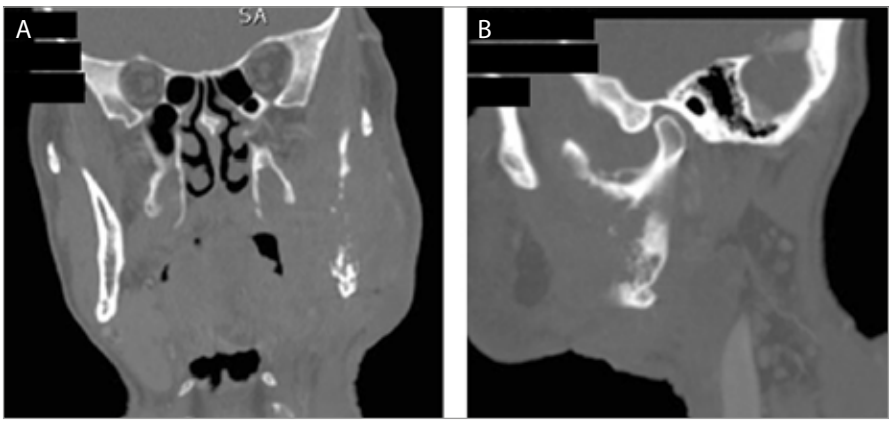


Fig. 4. Coronal (A) and sagittal (B) CT images of the same patient.

niques when evaluating the presence of bone invasion. However, which one of these is better still remains controversial. The results of Vidiri et al [35] showed that MRI was more sensitive (93%) when evaluating the presence of mandibular bone invasion in comparison with CT (70%), with the same specificity of both techniques (82%), even though the difference was not statistically significant, probably due to a small group of patients. Similarly, Wiener et al [36] described a higher sensitivity of MRI (100%) compared to CT (71%) with the same specificity (93% and 96% respectively), the differences were also not statistically significant. On the other hand, when evaluating bone invasion into mandible, Imaizumi et al [37] pointed out the potential pitfalls of MRI, which represents a significant number of false positive cases. In his study, the MRI sensitivity and specificity was 96% and 54% and the CT sensitivity and specificity was 100% and 88%, respectively. Silva et al [38] also reported the low specificity of MRI in comparison with CT as a crucial difference between these imaging techniques. Abd El-Hafez et al [39] compared PET/CT and MRI. In his study, the sensitivity and the specificitity for PET/CT was 78% and 83%, and those for MRI were 97% and 61%, respectively. Due to the higher specificity, PET/CT may complement the role of MRI in the diagnosing of bone invasion by oral carcinoma. The author suggested that in dentate patients with positive MRI findings, a negative PET/CT may be useful to rule out bone marrow invasion [39]. Hakim et al [40] studied the possibility of using CBCT when evaluating bone invasion. In their study, CBCT showed a higher sensitivity in comparison with the CT. According to the authors, CBCT represents an alternative imaging technique, which could be combined with another imaging technique of soft tissues such as MRI [40].

Conclusion

Bone invasion by oral squamous cell carcinoma is most commonly present in tumours close to the bone or in bigger and more advanced tumours and it is considered to be an adverse prognostic factor. Activated osteoclasts play a crucial role in the bone invasion process. From the viewpoint of histology, there are three patterns of bone invasion – erosive, mixed and infiltrative. The preoperative evaluation of the presence of bone involvement is important for planning the surgery. Despite all advances in the diagnosis and treatment, bone invasion which is caused by oral squamous cell carcinoma represents a diagnostic and therapeutic problem.

Roles of authors: All authors have been actively involved in the planning, preparation, analysis and interpretation of the findings, enactment and processing of the article with the same contribution.

Conflict of interests: The authors state that there are no conflicts of interest regarding the publication of this article. The authors declare that this study has received no financial support.

References

1. Wong RJ., Keel SB., Glynn RJ., et al. Histological patter of mandibular invasion by oral squamous cell carcinoma. *Laryngoscope* 2000, 110(1): 65–72.
2. Warnakulasuriya S. Global epidemiology of oral and oropharyngeal cancer. Oral Oncol. 2009, 45(4–5): 309–316.
3. Jimi E., Furuta H., Matsuo K., et al. The cellular and molecular mechanisms of bone invasion by oral squamous cell carcinoma. *Oral Dis.* 2011, 17(5): 462–468.
4. Kumar M., Nanavati R., Modi TG., et al. Oral cancer: Etiology and risk factors: a review. *J Cancer Res Ther.* 2016, 12(2): 458–463.
5. Castellsagué X., Alemany L., Quer M., et al. HPV involvement in head and neck cancers: comprehensive assessment of biomarkers in 3680 patients. *J Natl Cancer Inst.* 2016, 108(6): djv403.
6. Ord RA., Sarmadi M., Papadimitrou J. A comparison of segmental and marginal bony resection for oral squamous cell carcinoma involving the mandible. *J Oral Maxiloofac Surg*. 1997, 55(5): 470–477.
7. Rivera C. Essentials of oral cancer. *Int J Clin Exp Pathol*. 2015, 8(9): 11884–11894.
8. Quan J., Johnson NW., Zhou G., et al. Potential molecular targets for inhibiting bone invasion by oral squamous cell carcinoma: a review of mechanisms. *Cancer Metastasis Rev.* 2012, 31(1–2): 209–219.
9. Rabelo GD., Coutinho-Camillo C., Kowalski LP., et al. Evaluation of cortical mandibular bone in patients with oral squamous cell carcinoma. *Clin Oral Investig.* 2018, 22(2): 783–790.
10. Brown JS., Lowe D., Kalavrezos N., et al. Patterns of invasion and routes of tumor entry into the mandible by oral squamous cell carcinoma. *Head Neck.* 2002, 24(4): 370–383.
11. Pandey M., Rao LP., Das SR., et al. Patterns of mandibular invasion in oral squamous cell carcinoma of the mandibular region. *World J of Surg Oncol.* 2007, 5: 12.
12. Slootweg PJ., Müller H. Mandibular invasion by oral squamous cell carcinoma. *J Craniomaxillofac Surg.* 1989, 17(2): 69–74.
13. Brown JS., Browne RM. Factors influencing the patterns of invasion of the mandible by oral squamous cell carcinoma. *Int J Oral Maxillofac Surg.* 1995, 24(6): 417–426.
14. Huntley TA., Busmanis I., Desmond P., et al. Mandibular invasion by squamous cell carcinoma: a computed tomographic and histological study. *Br J Oral Maxillofac Surg.* 1996, 34(1): 69–74.
15. Ebrahimi A., Murali R., Gao K., et al. The prognostic and staging implications of bone invasion in oral squamous cell carcinoma. *Cancer.* 2011, 117(19): 4460–4467.
16. Kuk SK., Yoon HJ., Hong SD., et al. Staging significance of bone invasion in small-sized (4 cm or less) oral squamous cell carcinoma as defined by the American Joint Committee on Cancer. *Oral Oncol.* 2016, 55: 31–36.
17. Okura M., Yanamoto S., Umeda M., et al. Prognostic and staging implications of mandibular canal invasion in lower gingival squamous cell carcinoma. *Cancer Med.* 2016, 5(12): 3378–3385.
18. Mücke T., Hölzle F., Wagenpfeil S., et al. The role of tumour invasion into the mandible of oral squamous cell carcinoma. *J Cancer Res Clin Oncol.* 2011, 137(1): 165–171.
19. Petrovic I., Montero PH., Migliacci JC., et al. Influence of bone invasion on outcomes after marginal mandibulectomy in squamous cell carcinoma of the oral cavity. *J Craniomaxillofac Surg.* 2017, 45(2): 252–257.
20. Tada T., Shin M., Fukushima H., et al. Oral squamous cell carcinoma cells modulate osteoclast function by RANKL-dependent and -independent mechanisms. *Cancer Lett.* 2009, 274(1): 126–131.
21. Tada T., Jimi E., Okamoto M., et al. Oral squamous cell carcinoma cells induce osteoclast differentiation by suppression of osteoprotegerin expression in osteoblasts. *Int J Cancer.* 2005, 116(2): 253–262.
22. Sato K., Lee JW., Sakamoto K., et al. RANKL synthesized by both stromal cells and cancer cells plays a crucial role in osteoclastic bone resorption induced by oral cancer. *Am J Pathol.* 2013, 182(5): 1890–1899.
23. Zhang X., Junior CR., Liu M., et al. Oral squamous carcinoma cells secrete RANKL directly supporting osteolytic bone loss. *Oral Oncol.* 2013, 49(2): 119–128.

24. Raggatt LJ., Partridge NC. Cellular and molecular mechanisms of bone remodelling. *J Biol Chem*. 2010, 285(33): 25103–25108.
25. Theoleyre S., Wittrant Y., Tat SK., et al. The molecular triad OPG/RANK/RANKL: involvement in the orchestration of pathophysiological bone remodelling. *Cytokine Growth Factor Rev.* 2004, 15(6): 457–475.
26. Boyce BF., Xing L. Functions of RANKL/RANK/OPG in bone modelling and remodelling. *Arch Biochem Biophys*. 2008, 473(2): 139–146.
27. Russmueller G., Moser D., Würger T., et al. Upregulation of osteoprotegerin expression correlates with bone invasion and predicts poor clinical outcome in oral cancer. *Oral Oncol.* 2015, 51(3): 247–253.
28. Ishikuro M., Sakamoto K., Kayamori K., et al. Significance of the fibrous stroma in bone invasion by human gingival squamous cell carcinomas. *Bone* 2008, 43(3): 621–627.
29. Totsuka Y., Usui Y., Tei K., et al. Mandibular involvement by squamous cell carcinoma of the lower alveolus: analysis and comparative study of histological and radiologic features. *Head Neck*. 1991, 13(1): 40–50.
30. Carter RL., Tsao SW., Burman JF., et al. Patterns and mechanisms of bone invasion by squamous carcinomas of the head and neck. *Am J Surg.* 1983, 146(4): 451–455.
31. Sarrión Pérez MG., Bagán JV., Jiménez Y., et al. Utility of imaging techniques in the diagnosis of oral cancer. *J Craniomaxillofac Surg.* 2015, 43(9): 1880–1894.
32. Zupi A., Califano L., Maremonti P., et al. Accuracy in the diagnosis of mandibular involvement by oral cancer. *J Craniomaxillofac Surg.* 1996, 24(5): 281–284.
33. Rao LP., Das SR., Mathews A., et al. Mandibular invasion in oral squamous cell carcinoma: investigation by clinical examination and orthopantomogram. *Int J Oral Maxillofac Surg.* 2004, 33(5): 454–457.
34. Gu DH., Yoon DY., Park CH., et al. CT, MR, (18) F-FDG PET/CT, and their combined use for the assessment of mandibular invasion by squamous cell carcinomas of the oral cavity. *Acta Radiol.* 2010, 51(10): 1111–1119.
35. Vidiri A., Guerrisi A., Pellini R., et al. Multi-detector row computed tomography (MDCT) and magnetic resonance imaging (MRI) in the evaluation of the mandibular invasion by squamous cell carcinomas (SCC) of the oral cavity. Correlation with pathological data. *J Exp Clin Cancer Res.* 2010, 29(1): 73.
36. Wiener E., Pautke C., Link TM., et al. Comparison of 16-slice MSCT and MRI in the assessment of squamous cell carcinoma of the oral cavity. *Eur J Radiol.* 2006, 58(1): 113–118.
37. Imaizumi A., Yoshino N., Yamada I., et al. A potential pitfall of MR imaging for assessing mandibular invasion of squamous cell carcinoma in the oral cavity. *AJNR Am J Neuroradiol.* 2006, 27(1): 114–122.
38. Silva M., Zambrini EI., Chiari G., et al. Pre-surgical assessment of mandibular bone invasion from oral cancer: comparison between different imaging techniques and relevance of radiologist expertise. *Radiol Med.* 2016, 121(9): 704–710.
39. Abd El-Hafez YG., Chen CC., Ng SH., et al. Comparison of PET/CT and MRI for the detection of bone marrow invasion in patients with squamous cell carcinoma of the oral cavity. *Oral Oncol.* 2011, 47(4): 288–295.
40. Hakim SG., Wieker H., Trenkle T., et al. Imaging of mandible invasion by oral squamous cell carcinoma using computed tomography, cone-beam computed tomography and bone scintigraphy with SPECT. *Clin Oral Investig.* 2014, 18(3): 961–967.

David Král, MD
Department of Oral and Maxillofacial Surgery
Faculty of Medicine
Palacký University Olomouc
and University Hospital Olomouc
I.P.Pavlova 185/6
779 00 Olomouc
Czech Republic
e-mail: david.kral@fnol.cz

Submitted: 12.6.2021
Accepted: 30.7.2021

doi: 10.48095/ccachp2021145

Three-dimensional navigation in maxillofacial surgery – the way to minimize surgical stress and improve accuracy in fibula free flap and Eagle's syndrome surgical procedures

L. Czakó[1], M. Vavro[1], B. Dvoranová[1], M. Soviš[1], K. Šimko[1], A. Thurzo[2], B. Gális[1], F. Sándor[3]

[1] Department of Oral and Maxillofacial Surgery of Medical Faculty of Comenius University and University Hospital Bratislava, Bratislava, Slovak Republic
[2] Department of Simulation and Virtual Medical Education of Medical Faculty of Comenius University Bratislava, Bratislava, Slovak Republic
[3] Department of Pulmonary Medicine and Pathophysiology of Medical Faculty of Comenius University Bratislava, Bratislava, Slovak Republic

Summary

Background: Surgical navigation with three-dimensional (3D) printing techniques presents two major advantages: First, from a technical aspect, it facilitates orientation in target anatomical structures resulting in improvement of the accuracy of surgery. Moreover, it shortens the time of complex surgical interventions by preparing the exact position of customized autologous grafts with fixation devices. Second, from a clinical point of view, it also lessens the impact of surgical stress to adjacent tissues by decreasing the duration of surgery. **Material and methods:** Two maxillofacial procedures were evaluated in this study using 3D navigation and planning approach – resection of the styloid process due to Eagle's syndrome and microvascular mandibular reconstruction with the fibula free flap. All patients who underwent these procedures were divided into two groups (with or without 3D navigation). Results: In the Eagle's syndrome group procedure independent t-test showed significant difference in the operating time between group 1 (M = 148; SD = 0) and group 2 (M = 78; SD = 4.24) t (1) = 13.472; P = 0.047. There was no significant difference in the duration of postoperative hospitalization (2 days), which was equal in all patient groups. Regarding the fibula free flap procedure, the independent t-test revealed significant difference in operating time with (M = 8: 40 : 25; SD = 0 : 58 : 07) and without 3D printing guides (M = 10 : 43 : 15; SD = 3 : 04 : 32) t (14)=2.133, P = 0.051. Similarly, there was no significant difference between groups (group 1 M = 15.5; SD = 0,71; group 2 M = 13; SD = 1,63) in the duration of postoperative hospitalization time t (4) =1,98; P = 0.119. **Conclusion:** In summary, reduction in operation time in Eagle's syndrome and in microvascular mandibular reconstruction with the fibula free flap group mitigates the surgical stress on target tissues enabling faster tissue healing and quicker recovery.

Key words

Eagle's syndrome – head and neck carcinoma – head and neck surgery – fibula free flap – 3D navigation

Czakó L., Vavro M., Dvoranová B., et al. Three-dimensional navigation in maxillofacial surgery – the way to minimize surgical stress and improve accuracy in fibula free flap and Eagle's syndrome surgical procedures. Acta Chir Plast. 2021, 63(3): 145–149.

Introduction

Three-dimensional (3D) printing techniques, also known as additive manufacturing (AM), have been developing for the past three decades since 1986 [1]. However, the level of precision and accuracy required for clinical use was achieved only recently [2]. In combination with anatomically sensitive clinical imaging techniques such as MRI or CT scans, 3D printing technology in maxillofacial surgery offers important assistance in prosthetic rehabilitation, reconstruction and regeneration [3]. Low-cost 3D printing models have been used in medicine in many variations, including preoperative planning, surgical intraoperative guidance and advanced medical education [1,4]. These synthetic models improve our understanding of preoperative anatomy in individual cases, allow us to optimize our surgical approaches and introduce novel techniques tailored to a specific patent. This results in the reduction of operative time and surgical stress and minimization of perioperative errors [5,6]. In this clinical study, we present two reconstructive methods assisted by 3D printing. We were able to achieve patient-directed customized anatomical approach and identify major structural landmarks during

preoperative planning. In addition, 3D printing technique enabled us to predict the stability and prepare shapes of the used alloplastic materials [3,6].

Material and methods

In this study, we used 3D printed models for navigation and planning during surgical procedures of styloid process and fibula free flap reconstruction. Printed models helped in exact location of the styloid process resection site without damaging the surrounding anatomical structures. Compared to traditional methods, in patients undergoing mandibular resection due to malignancy, 3D models helped to identify the cutting edges and major landmarks used in mandibular reconstructive interventions.

A Form2 3D printer (Formlabs) was used to create all preoperative models. A PreForm software was used to design 3D models of temporal bone, mandible and other anatomical structures. Written informed consent was obtained from the patients undergoing surgical interventions after detailed explanation of the risks and benefits.

Results

Styloid process resection group

For the past 3 years, we identified and enrolled a total of 8 patients with 15 elongated styloid processes (Eagle's syndrome) in this study. Seven of them underwent bilateral resection of an elongated styloid process and one patient underwent unilateral resection. Three patients had surgery without the preoperative model approach (group 1) and five patients underwent surgical procedure using the preoperative model of patient specific 3D printing of bony structures (group 2) (Fig. 1). The duration of surgery in minutes and the length of postoperative hospitalization in days were measured.

The model was examined to determine whether specific anatomical structures were located correctly and were of the appropriate shape. All 3D printed models were scanned by CT with the same parameters as those of the original temporal bone and mandible. The reproducibility of the structures such as the anatomical position, length and form of styloid process, location of the stylomastoid foramen, transversal process of the atlas and distance from the ascending ramus of the mandible were evaluated by comparing CT images of the 3D models to those of the originals. Subsequently, we used this exact 3D model preoperatively as a spatial navigation tool to perform exact resection of the styloid process.

Fig. 1. The skull model fabricated by using 3-dimentional printing technology reveals bilateral elongated styloid processes.

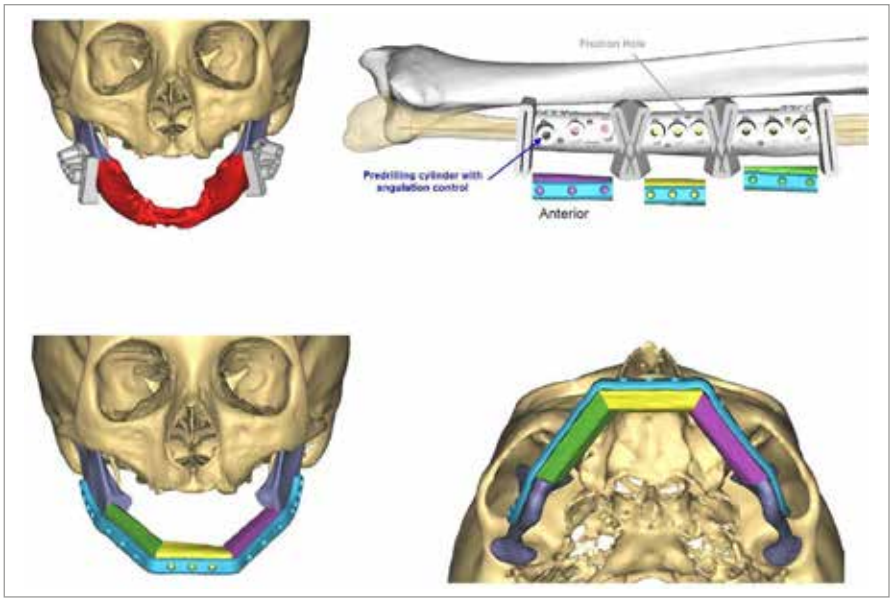


Fig. 2. Virtual surgical planning of the mandibular reconstruction with fibula free flap. The guides for osteotomies (up) perform perfect fitting fibular segments for further reconstruction exactly in the defect side. The titanium plate (down) is customized and prepared before surgery, it is made based on virtual surgical planning and adapted on the segments.

The temporal bone and the mandible models were printed from the PLY file from biocompatible resin, in resolution of 50 microns, on a full-color FORM 2 3D printer (Formlabs Inc., Sommerville, Massachusetts, USA).

An independent t-test showed a significant difference in the operating time between group 1 (M = 148; SD = 0) and group 2 (M = 78; SD = 4.24) t (1) = 13.472; P = 0.047. There was no significant difference in the postoperative hospitalization duration (2 days), which was equal in all patient groups.

Fibula free flap reconstruction group

The 3D printed models of mandible and cutting guides for fibula resection were performed 2 weeks prior to the surgery (TruMatch, Materialise NV, Leuven, Belgium) (Fig. 2). We enrolled a total of 16 patients in this cohort. The locations of cutting lines, shape of the reconstruction, position of plate and screws was discussed in a real-time internet video conference between the manufacturer and the operating team. All patients underwent reconstruction of mandible after malignant tumor resection (1–3 segments). After dividing the patients to regular surgery (group 1–2 patients) and 3D printing assisted groups (group 2–4 patients), we assessed the same parameters as in the styloid process group – the length of surgical intervention in minutes and postoperative hospitalization duration in days. The created model was used as a guide to identify optimal cutting lines. An independent t-test revealed a significant difference in operating time in 3D printing guides group (M = 8 : 40 : 25; SD = 0 : 58 : 07) and without 3D printing guide (M = 10 : 43 : 15; SD = 3 : 04 : 32); t (14) = 2.133, P = 0.051. There was no significant difference between the groups (group 1: M = 15.5; SD = 0.71; group 2. M = 13; SD = 1.63) in the duration of postoperative hospitalization t (14) = 1.98; P = 0.119.

Discussion

Eagle's or stylohyoid syndrome is a generally unknown and rarely identified anatomical and clinical condition. It involves the elongation of the styloid process (> 4 cm) or calcification of the stylohyoid ligament [7,8]. It is characterized by symptoms of recurrent or permanent throat and neck pain, pharyngeal foreign body sensation, dysphagia and bilateral otalgia [9,10]. The symptoms of Eagle's syndrome are nonspecific and may mimic tumors, infection, or neuralgia what makes it quite difficult to establish the correct diagnosis based solely on clinical manifestation [11]. Eagle's syndrome has been described as a pain syndrome associated with an elongated styloid. The congenital variant, often described as stylohyoid syndrome, has been described as a syndrome with pain and symptoms of carotid compression (syncope, presyncope, and even transient ischemic attacks) caused by an ossified stylohyoid ligament [9,12]. The incidence of abnormal stylohyoid length ranges from 4% to 28% [13,14]. The incidence is higher if calcification of the stylohyoid complex is included in 22–84% [15,16]. These symptoms can be associated with the compression of the anatomic structures that are closely related to the styloid process and the stylohyoid ligament such as facial, accessory, hypoglossal, vagal, and glossopharyngeal nerves, the internal jugular vein, and the internal carotid artery [17].

A free flap reconstruction has been a useful technique in various instances regarding maxillofacial surgery. A fibula free flap has been known to be a well-established surgical correction option in cases of mandibular reconstruction for the past 30 years [18]. This technique provides low donor-side morbidity, adequate portion of osseous graft, and a satisfactory postoperative function leading to overall improvement of the quality of life. Virtual surgical planning (VSP) allows to perform precise osteotomies on the affected site and fit the segments of fibula in the individual prefabricated plates [19,20]. Although free flap reconstruction with fibular flap is technically feasible, yet it is still undeniably time and manpower consuming. Moreover, the postoperative period confers a risk of flap failure with added potential of a donor-side morbidity [21]. Various approaches such as 3D printing technologies are aimed at decreasing the impact of time-consuming surgical procedures on tissues and organs [6,19,22]. These techniques can be easily incorporated into specialty training curricula due to their relatively shallow learning curve. In addition, they allow for precise, anatomically correct bony reconstruction and ultimately decrease the overall surgical time [23].

Effects of surgery on tissues

Direct effects of surgery in the head and neck region are primarily related to cellular injury. In maxillofacial surgery, both direct and indirect surgical injury are present. Direct surgical injury occurs through surgical access, organ mobilization, excision, and dissection. Greater degrees of tissue injury lead to higher levels of inflammatory mediator and cytokine release, which drive immunologic, metabolic, and hormonal processes in the body known as the surgical stress response [24].

Although the development of minimally invasive surgery, robotic techniques and endoscopic interventions have greatly decreased direct tissue injury at the time, open approaches are still necessary to achieve the desired treatment goals and outcomes. Much of the direct tissue injury is caused by cervical/facial trauma or extensive scars, which may be reduced through changing incision orientation or minimizing the size of the incision [25].

Indirect injury occurs through several methods including alterations in tissue perfusion, microvascular changes associated with blood loss, and from using

different anesthetic techniques. Since tissue oxygen delivery is determined by hemoglobin concentration, cardiac output, and oxygen saturation, a decrease in hemoglobin levels will directly impact the metabolic function on a cellular level. In addition, decreased oxygen delivery can lead to tissue and organ dysfunction by means of tissue hypoxemia and hypoperfusion causing the development of systemic inflammatory response syndrome and sepsis [26].

Direct surgical manipulation in the head and neck region such as retraction, ligation of vessels, removal of tissues, nerves or organ components can also negatively affect tissue perfusion. Direct injury by mechanical means causes induction of various inflammatory cascades leading to significant cellular dysfunction.

During surgical interventions, patient positioning can also pose a potential threat to the tissue microvascular environment. Prolonged unphysiological positioning, whether head up or down or various tilted positions, causes intravascular fluid shifts having deleterious effects on tissue perfusion.

Surgical stress response

Direct or indirect injuries lead to cytokine and inflammatory mediator release. In response to cellular injury, neutrophils and macrophages produce proinflammatory cytokines including tumor necrosis factor alpha (TNF-α), and several interleukins (IL-1, IL-6, IL-8) [27]. These cytokines induce the liver to increase synthesis of acute phase proteins such as C-reactive protein (CRP), albumin, ferritin, transferrin, and fibrinogen. The levels of these acute phase reactants, particularly IL-6 and CRP, correlate with the magnitude of the stress response and the development of the systemic inflammatory response [28]. Several studies have demonstrated that endoscopic and robotic surgeries are associated with lower levels of IL-6 and CRP production when compared with traditional open procedures. Patients with higher levels of proinflammatory markers are more likely to develop postoperative complications [29]. Along with the upregulation of proinflammatory cytokines and acute phase proteins in response to surgical stress, there is also activation of the hypothalamic-pituitary-adrenal axis that leads to an elevation in counter-regulatory stress hormones including cortisol, growth hormone, glucagon, and catecholamines. One of the main surgical concerns regarding the hormonal stress response is the development of insulin resistance through the combination of catecholamine release and impaired function of the immune system [30].

Catabolic hormones and inflammatory mediators also lead to salt and water retention in response to a surgical injury. As reported in prior publications, mitochondrial activity is suppressed with an overall reduction of ATP levels. Increased inflammatory response following surgery leads to elevated production of reactive oxygen species (ROS). ROS are able to damage lipids, proteins, and even DNA, which leads to impaired vascular permeability [31]. Cell disruption from direct surgical manipulation releases several intracellular mediators including potassium, bradykinin, heat shock proteins, various cytokines/chemokines and nerve growth factors. These have been reported to cause peripheral sensitization of nociceptors. In addition to these proinflammatory mediators, calcitonin gene-related peptide and substance P also sensitize nociceptors in adjacent tissues that were not directly injured by surgical trauma. Ultimately, this leads to central sensitization through NMDA receptors in the dorsal horn of the spinal cord and can lead to the development of hyperalgesia, allodynia, and possible chronic postsurgical orofacial pain [25].

Conclusion

Reducing operating time, decreasing the impact of surgical stress and minimizing the length of hospital stay should be the aim of every surgery. Manipulation of tissues in the head and neck region is much dependent on being familiar with the major anatomical landmarks. In case of styloid process surgery, it is crucial to avoid additional damage of the surrounding tissues (facial, accessory, hypoglossal, vagal, the internal jugular vein, and the internal carotid artery). Detailed preoperative planning by recognizing and labeling the major bone structures has shown to significantly improve the accuracy of the surgical intervention.

Our statistical analysis reveals a significant difference in measured parameters within both procedures, fibula free flap reconstructive surgery group and in the Eagle's syndrome group, every operation with 3D navigation had a shorter absolute duration of surgery than the traditional procedure without 3D navigation model. This difference was also noted in a subset of patients who underwent reconstruction of at least three or more fibular segments in the fibula free flap group. High proficiency in identifying the individual anatomy helps to avoid errors during surgery, reduces the operative time burden and specifies the best location for safe resection of the tumor. Overall reduction of surgical time is potentially beneficial in mitigating the impact of surgical stress and leads to improved tissue healing with quicker recovery.

Roles of authors: An investigator of this study was responsible for enrolling patients in the study, following the protocol and postoperative assessment. All authors have been actively involved in the planning, preparation, analysis and interpretation of the findings, enactment and processing of the article with the same contribution

Conflict of interest: This study did not receive a specific grant from any funding agencies in the public, commercial, or not-for-profit sectors. The authors have declared no conflict of interest.

Disclosure: All procedures performed in this study involving human participants were in accordance with ethical standards of the institutional and/or national research committee and with the Helsinki declaration and its later amendments or comparable ethical standards.

References

1. Zhong N., Zhao X. 3D printing for clinical application in otorhinolaryngology. *Eur Arch Otorhinolaryngol*. 2017, 274(12): 4079–4089.

2. Zadpoor AA., Malda J. Additive manufacturing of biomaterials, tissues, and organs. *Ann Biomed Eng*. 2017, 45(1): 1–11.

3. Nyberg EL., Farris AL., Hung BP., et al. 3D-printing technologies for craniofacial rehabilitation, reconstruction, and regeneration. *Ann Biomed Eng*. 2017, 45(1): 45–57.

4. Marconi S., Pugliese L., Botti M., et al. Value of 3D printing for the comprehension of surgical anatomy. Surg Endosc. 2017, 31(10): 4102–4110.

5. Aldaadaa A., Owji N., Knowles J. Three--dimensional printing in maxillofacial surgery: hype versus reality. *J Tissue Eng*. 2018, 9: 2041731418770909.

6. Patel A., Levine J., Brecht L., et al. Digital technologies in mandibular pathology and reconstruction. *Atlas Oral Maxillofac Surg Clin North Am*. 2012, 20(1): 95–106.

7. Montalbetti L., Ferrandi D., Pergami P., et al. Elongated styloid process and Eagle's syndrome. *Cephalalgia*. 1995, 15(2): 80–93.

8. Eagle WW., Durham NC. Elongated styloid processes. Report of two cases. *Arch Otolaryngol Head Neck Surg*. 1937, 25(5): 584–587.

9. Colby CC., Del Gaudio JM. Stylohyoid complex syndrome. *Arch Otolaryngol Neck Surg*. 2011, 137(3): 248–252.

10. Eagle WW. Elongated styloid process: Further observation and a new syndrome. *Arch Otolaryngol*. 1948, 47(5): 630–640.

11. Blomgren K., Qvarnberg Y., Valtonen H. Spontaneous fracture of an ossified stylohyoid ligament. J Laryngol Otol. 1999, 113(9): 854–855.

12. Farhat HI., Elhammady MS., Ziayee H., et al. Eagle syndrome as a cause of transient ischemic attacks. *J Neurosurg*. 2009, 110(1): 90–93.

13. Eagle WW., Durham NC. Elongated styloid process: symptoms and treatment. *AMA Arch Otolaryngol*. 1958, 67(2): 172–176.

14. Kaufman SM., Elzay RP., Irish EF. Styloid process variation: radiologic and clinical study. *Arch Otolaryngol*. 1970, 91(5): 460–463.

15. Badhey A., Jategaonkar A., Anglin Kovacs AJ., et al. Eagle syndrome: a comprehensive review. *Clin Neurol Neurosurg*. 2017, 159: 34–38.

16. Ferrario VF., Sigurta D., Daddona A., et al. Calcification of the stylohyoid ligament: Incidence and morphoquantitative evaluations. *Oral Surg Oral Med Oral Pathol*. 1990, 69(4): 524–529.

17. Piagkou MN., Anagnostopoulou S., Kouladouros K., et al. Eagle's syndrome: a review of the literature. *Clin Anat*. 2009, 22(5): 545–558.

18. Hidalgo DA. Fibula Free Flap: A new method of mandible reconstruction. *Plast Reconstr Surg*. 1989, 84(1): 71–79.

19. Patel SY., Kim DD., Ghali GE. Maxillofacial reconstruction using vascularized fibula free flaps and endosseous implants. *Oral Maxillofac Surg Clin North Am*. 2019, 31(2): 259–284.

20. Pietruski P., Majak M., Świątek-Najwer E., et al. Navigation-guided fibula free flap for mandibular reconstruction: A proof of concept study. *J Plast Reconstr Aesthetic Surg*. 2019, 72(4): 572–580.

21. Lin YS., Liu WC., Wang KY., et al. Obliquely--arranged double skin paddles: A novel design to reconstruct extensive head and neck defects with a single fibula or peroneal flap. *Microsurgery*. 2019, 39(2): 108–114.

22. Morita M., Saeki H., Ito S., et al. Technical improvement of total pharyngo-laryngo-esophagectomy for esophageal cancer and head and neck cancer. *Ann Surg Oncol*. 2014, 21(5): 1671–1677.

23. Levine JP., Patel A., Saadeh PB., et al. Computer-aided design and manufacturing in craniomaxillofacial surgery: The new state of the art. *J Craniofac Surg*. 2012, 23(1): 288–293.

24. Scott MJ., Miller TE. Pathophysiology of major surgery and the role of enhanced recovery pathways and the anesthesiologist to improve outcomes. *Anesthesiol Clin*. 2015, 33(1): 79–91.

25. Feldheiser A., Aziz O., Baldini G., et al. Enhanced Recovery After Surgery (ERAS) for gastrointestinal surgery, part 2: consensus statement for anaesthesia practice. *Acta Anaesthesiol Scand*. 2016, 60(3): 289–334.

26. Stephan RN., Kupper TS., Geha AS., et al. Hemorrhage without tissue trauma produces immunosuppression and enhances susceptibility to sepsis. *Arch Surg*. 1987, 122(1): 62–68.

27. Baigrie RJ., Lamont PM., Kwiatkowski D., et al. Systemic cytokine response after major surgery. *Br J Surg*. 1992, 79(8): 757–760.

28. Watt DG., Horgan PG., McMillan DC. Routine clinical markers of the magnitude of the systemic inflammatory response after elective operation: A systematic review. *Surgery* 2015, 157(2): 362–380.

29. Podgoreanu MV., Michelotti GA., Sato Y., et al. Differential cardiac gene expression during cardiopulmonary bypass: Ischemia-independent upregulation of proinflammatory genes. *J Thorac Cardiovasc Surg*. 2005, 130(2): 330–339.

30. Carli F. Considérations physiologiques sur les programmes de Récupération rapide après la chirurgie (RRAC): implications de la réponse au stress. *Can J Anesth*. 2015, 62(2): 110–119.

31. Chowdhury AH., Lobo DN. Fluids and gastrointestinal function. *Curr Opin Clin Nutr Metab Care*. 2011, 14(5): 469–476.

Assoc. Prof. Ladislav Czakó., MD. Phd., MPH.
Department of of Oral and Maxillofacial Surgery of Medical Faculty of Comenius University and University Hospital Bratislava
Ružinovská 6
826 06 Bratislava, Slovakia
e-mail: czako@ionline.sk

Submitted: 30.5.2021
Accepted: 23.8.2021

Is it a second scrotum?

G. Vissers[1,2], K. Smets[3], T. Tondu[1,2], F. Thiessen[1,2]

[1] Department of Plastic, Reconstructive and Aesthetic Surgery, University Hospital Antwerp, Edegem, Belgium
[2] Faculty of Medicine and Health Sciences, Antwerp University, Wilrijk, Belgium
[3] Department of Dermatology, GZA Sint-Augustinus Hospital, Wilrijk, Belgium

Dear Sir,

We would like to share a peculiar presentation of a superficial lipomatous naevus at the right inner thigh of a male patient, resembling the patient's nearby located scrotum.

A 35-year-old man presents with a slowly growing lesion on his right inner thigh. The lesion has been present for a few years. It makes the patient self-conscious but causes no other symptoms. The patient has no previous medical history and no family history of skin disease.

Clinical examination reveals a saccular lesion on the right inner thigh. It is a solitary, soft and skin-coloured lesion, resembling the patient's nearby-located scrotum (Fig. 1). Ultrasound imaging shows a subcutaneous fatty content with no deep connections and no visible vasculature.

Resection under local anaesthesia is performed for cosmetic reasons (Fig. 2). Histopathological examination reveals a superficially subcutaneously located lipomatous lesion with mature, white adipose cells and polypoid transformation, compatible with naevus lipomatosus cutaneous superficialis (also called superficial lipomatous naevus or "fat naevus"). There is no dysplasia and immunohistochemical staining with Murine Double Minute 2 (MDM2) to rule out liposarcoma is negative.

A superficial lipomatous naevus is an idiopathic, cutaneous hamartoma that was first described by Hoffman and Zurhelle in 1921 [1]. It is defined by the presence of the aggregates of mature, ectopic adipocytes among the collagen bundles of the dermis. Typically, the lesions are either congenital or present by the third decade of life with no sex predilection.

A superficial lipomatous naevus is clinically classified into two types: classical or solitary. The classical form presents as multiple clusters of soft, skin-coloured nodules that mainly occur in the pelvic-girdle area. They have a zosteriform pattern and may either be sessile or pedunculated. The solitary form presents as a single, pedunculated, skin-coloured lesion that may occur anywhere on the body [2].

A superficial lipomatous naevus can be left untreated as it is a benign condition. In our case, resection under local anaesthesia was performed for cosmetic reasons. Its resection is usually curative.

Financial disclosures: None of the authors has a financial interest in any of the products, devices, or drugs mentioned in this manuscript.

References

1. Hoffmann E, Zurhelle E. Über einen Naevus lipomatodes cutaneus superficialis der linken Glutäalgegend. *Archiv für Dermatologie und Syphilis* 1921, 130(1): 327–333.
2. Lynch FW, Goltz RW. Nevus lipomatosus cutaneus superficialis (Hoffmann-Zurhelle); presentation of a case and review of the literature. *AMA Arch Derm*. 1958, 78(4): 479–482.

Gino Vissers, MD
Department of Plastic, Reconstructive and Aesthetic Surgery
University Hospital Antwerp
Drie Eikenstraat 655
B-2650 Edegem
Belgium
e-mail: ginovissers@doctor.com

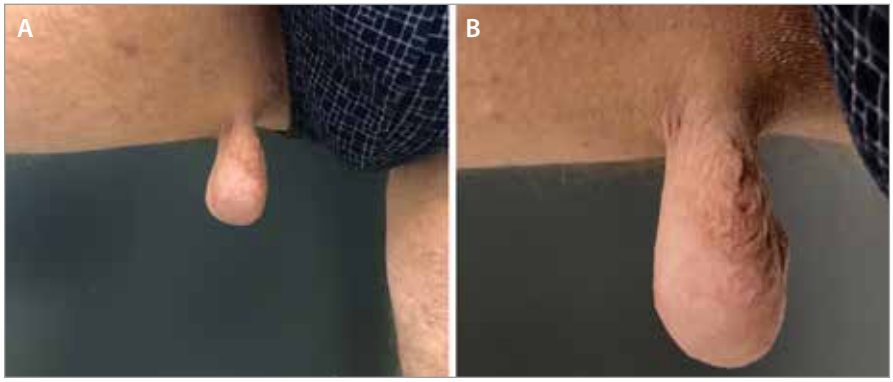


Fig. 1. Overview (A) and close-up (B) photos of the lesion at the patient's right inner thigh that has been present for a few years. The colour, texture and firmness mimic the patient's nearby-located scrotum.

Fig. 2. Intraoperative photo of the lesion that was successfully resected under local anaesthesia. No recurrence occurred.

Professor Radana Königová Prize awards

M. Tokarik

Department of Burns Medicine, 3rd Faculty of Medicine, Charles University and Teaching Hospital Královské Vinohrady, Prague, Czech Republic

On June 4, 2021, a meeting of the Committee of the Society of Burns Medicine of the Czech Medical Society of Jan Evangelista Purkinje was held in Brno. One extraordinary item was included in the programme agenda – the ceremony of awarding the **Professor Radana Königová Prize** to the honoured personalities for the years 2019 and 2020, and retrospectively also for the year 2015. Due to long-term constraints related to the ongoing pandemic of COVID-19 disease, it was not possible to use the Society's annual conferences for this official occasion. The festive framework and importance of this event was documented by the presence of the representatives of the Faculty of Medicine of Masaryk University in Brno, Dean Prof. Martin Repko, MD, PhD, and Vice-Dean Prof. Zdeněk Kala, MD, PhD.

The Prize bears the name of the pioneer; a founder of burns medicine, world-renowned Prof. Radana Königová, MD, CSc., who passed away in 2014. Since 2015, the Committee of the Society of Burns Medicine bestows this Prize upon a person or organization that has greatly contributed to the development, promotion or reputation of burns medicine in the Czech Republic and abroad, and/or as manifestation of respect to the personalities who follow the profound ethical and humanitarian legacy of Prof. Königová by their acts. The Czech Society of Burns Medicine also values the results of scientific research work as well as benefits for clinical practice in prevention, pathology, comprehensive treatment, and rehabilitation of patients with burns injuries (Tab. 1).

The first recipient of the award was **Yvona Kaloudová, MD** in 2015, awarded during the annual conference of the Society in Velké Bílovice. However, the material representation of this prize in the form of a crystal obelisk with a 3D portrait of Prof. Königová had not been made at that time and could only be handed over now. In accordance with the nomination criteria, the prize was awarded for lifetime contribution to the field of burns medicine.

Dr. Kaloudová joined the 3rd Department of Surgery of the Trauma Hospital in Brno – Ponávka in 1984, where she worked as a general surgeon and simultaneously at the Emergency Rescue Service. In 1989, together with several colleagues who were involved in the treatment of burns, she moved to the Bohunice Hospital, where the Burns Centre, the forerunner of today's Department of Burns and Plastic Surgery, had been established. She devoted her entire professional career to this department and has been working there as the head of the divisions of standard and intermediate care since 1995. She worked in the committee of the Society of Burns Medicine for 18 years. She is a member of the European Burns Association (EBA) and the International Society for Burn Injuries (ISBI). She is a regular speaker at national and international conferences and has published numerous scientific reports. Dr. Kaloudová has contributed significantly to the development of professional guidelines for the treatment of burns in pre-hospital care. She was active in the campaign for prevention of childhood burns injuries. She has been involved in training young doctors and nurses for a long time. She is an example of a physician fully committed to her field and her patients.

The 2019 awardee was **Prof. Pavel Brychta, MD, CSc.**, a renowned personality of Czech burns medicine and plastic surgery. He has been working in the field continuously since 1987. After the establishment of the workplace in the Bohunice University Hospital, he has gradually passed through all positions from a secondary physician, through the deputy chief and later the head of the Centre for Burns, to the head of today's Department of Burns and Reconstructive Surgery at the Faculty of Medicine of Masaryk University, which he has established and led since 2001. Despite complicated postgraduate training, he managed to build a stable multidisciplinary

Tab. 1. Awardees of Professor Radana Königová Prize.

Year	Name	Workplace
2015	Yvona Kaloudová, MD	Brno
2016	Prof. Rajko Doleček, MD, DrSc.	Ostrava
2017	Monika Adámková, MD	Ostrava
2018	Josef Bláha, MD, CSc.	Prague
2019	Prof. Pavel Brychta, MD, CSc.	Brno
2020	Assoc. Prof. Leo Klein, MD, CSc.	Hradec Králové

team. He is a supervisor of postgraduate medical education. Under his supervision, seven PhD students defended their dissertations and one habilitation procedure was held. Prof. Brychta is very active in lecturing and publishing, he is the author and co-author of several monographs, including international ones. He has been the principal investigator of three major grant projects in the field of burns treatment research, one of which led to the gaining of a patent (cultured epidermal graft). Prof. Brychta is a member of several national and international professional societies. He has been a member of the Society of Burns Medicine since its inception, a long-standing member of the Committee, and was the Chairman between 2011 and 2017. He is a member of EBA, where he served on the Committee as Secretary, Vice-president and President (2009–2011). He is a member of ISBI where he served as Vice-president in 2008–2010. His continued and versatile professional activities and involvement in the Societies of Plastic Surgery, Aesthetic Surgery, the Society of Hand Surgery and the Society of Aesthetic and Laser Medicine have contributed significantly to the interconnected activities of several closely related surgical specialties along with burns medicine. He managed to achieve a similar interconnection in the organisational structure and functional content of the Burns Department in Brno. In this way, he represents burns medicine in the Czech medical environment, in public and in international professional circles.

The 2020 awardee was **Assoc. Prof. Leo Klein, MD, CSc.**, a significant personality of Czech burns medicine, plastic surgery and military medicine. He first encountered the treatment of burns at the surgical department of the Military Hospital Olomouc in 1976. In 1984, he moved to the Department of Military Surgery and the Second Department of Surgery of the Faculty of Medicine of Charles University and the Teaching Hospital in Hradec Králové, where the division of plastic surgery and burns treatment was newly being established. He started building the division and especially the functionally integrated burns unit from the very beginning. Within a few years, technical facilities and an interdisciplinary team were built up. The spectrum and numbers of patients treated were expanded, and in the late 1980s and 1990s the division served as a regional burns unit. After the Czech Republic joined NATO, Brig. Gen. Dr. Klein was sent abroad for a mission in 1999–2002, where he served as Medical Advisor to the Commander and Chief of the Medical Branch of the NATO Supreme Headquarters Allied Powers Europe (SHAPE) in Belgium. Between 2004 and 2008, he served as Head of the Department of Burns Medicine of the 3rd Faculty of Medicine, Charles University and Teaching Hospital Královské Vinohrady in Prague. Upon his return to his original workplace in 2008, he has been still working in Hradec Králové. Assoc. Prof. Klein is a member of several domestic and international professional societies. He is a founding member of our Society, where he has been a committee member for many years. He was the National Representative since 1994 and also the Regional Representative for Europe in ISBI in 2012–2014. He is a member of the EBA where he served three terms in the Executive Committee (2011–2017). He has authored and co-authored several monographs, numerous publications, and has conducted research projects and made more than 300 oral presentations. He has been intensively involved in teaching activities and has contributed to the training of several generations of young physicians. He serves on the editorial boards of national and foreign professional journals and is an external reviewer of other periodicals. Assoc. Prof. Klein has made a significant contribution to the representation of the field of burns medicine at home and abroad, in the conditions of civilian and military health care. He is an active promoter of Prof. Königová's legacy.

Fig. 1. Awardees of Professor Radana Königová Prize (from the left to the right): Leo Klein, Yvona Kaloudová, Pavel Brychta.

After the award ceremony, both representatives of the Faculty of Medicine held salutary speeches, in which they emphasized, among other things, the excellent cooperation of the Burns Centre in Brno with all clinics and departments within the Trauma Centre and the Faculty of Medicine of the Masaryk University. They also expressed their appreciation of the work of the Society of Burns Medicine, and its committee, in the context of the Czech Medical Society of J.E. Purkinje and Czech medicine as such.

On behalf of the entire Society of Burns Medicine, the members of the Committee thank all of the awardees (Fig. 1) for their work and wish them every success in their future life and work.

Monika Tokarik, MD, PhD
Chairwoman, Committee of the Society
of Burns Medicine CMS JEP
Dept. of Burns Medicine
University Hospital Královské Vinohrady
Šrobárova 50
100 34 Prague
Czech Republic
e-mail: monika.tokarik@fnkv.cz

ČESKÉ SOUHRNY

Fournierova gangréna po mužské obřízce – kazuistika a přehled literatury

M. Tripoli, E. Cammarata, A. Cordova

Úvod: Fournierova gangréna (FG) je nekrotizující fasciitida genitálií, perineální a perianální oblasti s významnou úmrtností. Potenciálně smrtelné onemocnění pochází z aerobních i anaerobních bakterií a primárně se vyskytuje u mužů. Většina případů Fournierovy gangrény je idiopatická nebo pochází z perineálních a genitálních kožních infekcí. Včasný chirurgický debridement nekrotických tkání a nasazení antibiotik je zásadní. **Případ:** Referujeme vzácný případ Fournierovy gangrény 57letého muže sekundárně po operaci obřízky. U pacienta se projevila bolestivým otokem šourku a hráze ve spojením s vysokou horečkou. Byla nasazena širokospektrální antibiotika a pacient podstoupil okamžitý chirurgický debridement, dalších celkem pět debridementů bylo provedeno během hojení, a to až do vyhojení ran. Ve druhé fázi jsme provedli rekonstrukci penisu s transplantací kůže v plné tloušťce s uspokojivým kosmetickým a funkčním výsledkem. **Závěr:** FG je nadále urgentní zdravotní problém spojený s vysokou úmrtností, který vyžaduje okamžitou léčbu. Pro zlepšení četnosti přežití je třeba více statistických údajů a standardní guidelines.

Rekonstrukční a estetická chirurgie prsu po orgánové transplantaci – systematický přehled, návrh nového protokolu a prezentace případů

R. B. Basso, M. E. Salto, H. F. Mayer

Úvod: Velký pokrok v transplantaci solidních orgánů (SOT) umožnil pacientům delší přežívání a užití kvalitního života po operaci. Rostoucí počet SOT a zlepšená míra dlouhodobého přežití vedou ke zvyšující se poptávce po plastických, estetických a rekonstrukčních operacích prsou. **Materiál a metody:** Bylo provedeno prohledání literatury podle pokynů „Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) a byly použity vyhledávací výrazy souvisejících s estetickou a rekonstrukční chirurgií prsu ve třech databázích: PubMed, Scopus a Google Scholar. Zahrnuté články byly analyzovány za účelem vyhledání dat, vč. věku pacienta, typu operace, transplantace orgánu, základních stavů spojených s transplantací orgánu, sledování, imunosupresivních léků a jejich vedlejších účinků, perioperační léčby a komplikacemi, které souvisely s plastickými operačními postupy na prsu. Ze zmíněných elektronických databází bylo získáno celkem 1 298 článků. Do tohoto systematického přehledu bylo nakonec zahrnuto 8 článků. V těchto článcích bylo uvedeno celkem 41 případů plastické operace prsu po orgánové transplantaci. Procedury byly estetické povahy v 26,8 % případů (11 ze 41 případů) a rekonstrukční v 73,2 % (30 ze 41 případů). Nebyla hlášena žádná úmrtí. **Závěr:** Přestože u příjemců SOT lze bezpečně provádět estetickou a rekonstrukční operaci prsu, je třeba vždy zohlednit dávku imunosuprese a celkový zdravotní stav pacientky s ohledem na délku a rozsah plánovaného výkonu. Z analýzy údajů z literatury není možné vyvodit statistické závěry, že míra komplikací chirurgického zákroku u imunosuprimovaných pacientů po transplantaci je stejná jako u normální, neimunosuprimované populace. Je třeba dalších validních klinických studií.

Charakteristika poranění prstů a návrh léčebného algoritmu dle doporučení centra chirurgie ruky v Mexico City

J. E. Telich-Tarriba, I. Santos-Gallegos, C. Arroyo-Berezowsky, A. Cardenas-Meji

Úvod: Špičky prstů jsou nejčastěji poraněné anatomické struktury na horní končetině. Cílem této práce je představit naše zkušenosti s léčbou poranění prstů. **Metody:** Byli zahrnuti všichni pacienti s poraněním prstů ošetření na Oddělení plastické a rekonstrukční chirugie všeobecné nemocnice „Dr Manuel Gea Gonzalez" v Mexiku od července 2010 do června 2015; jsou popsány jejich demografické charakteristiky, typ úrazu a jeho management. **Výsledky:** Do studie bylo zahrnuto celkem 1 265 pacientů, 75 % mužů. Průměrný věk prezentovaných byl 20,5 ± 16,46 let; nejčastěji postižená věková skupina byla mladší 15 let (46,7 %). Zranění vpravo a vlevo se vyskytla ve stejné míře (51 vs. 49 %). Nejčastěji zraněnými prsty byly třetí (27,2 %) a druhé (25,8 %). Osmdesát sedm procent pacientů mělo izolované poranění. Nejčastějším typem poranění byly amputace prstů na prstech u 620 případů (49 %), poté následovaly jednoduché tržné rány prstem (574 případů, 45 %) a poranění nehtového lůžka v 71 případech (5,6 %). Chirurgická léčba byla nutná v 95,8 % případů. **Závěr:** Nejčastějším důvodem vyšetření u akutních stavů ruky jsou poranění prstů. K dosažení nejlepších klinických výsledků je nezbytný systematický přístup k jejich léčbě.

Plazma obohacená o krevní destičky zlepšuje pooperační estetické výsledky po zákrocích maxilofaciální chirurgie

Y. Menchisheva, U. Mirzakulova, D. Usupova, G. Yermukhanova, Z. Rysbayeva

Úvod: Pooperační jizvy na obličeji po plastické a rekonstrukční operaci jsou viditelnými výsledky, které mohou vážně ovlivnit kvalitu života léčených pacientů. V současné době je plazma obohacená o krevní destičky (platelet-rich plasma – PRP) v medicíně široce používána ke zlepšení regenerace tkání. Cíl: Analyzovat estetické výsledky používání PRP v pozdním pooperačním období po maxilofaciálních zákrocích. **Materiál a metody:** Do této studie bylo zahrnuto 100 pacientů ve věku 18–60 let, kteří podstoupili plastickou a rekonstrukční operaci v maxilofaciální oblasti. Pacienti byli náhodně rozděleni do dvou skupin. Padesát pacientů v léčebné skupině dostávalo v době operace injekce PRP. Pacienti v kontrolní skupině nedostali žádné injekce. PRP byla injektována intradermálně po sutuře ran. Hodnocení výsledků léčby bylo prováděno planimetrií, programem Image J během 1 měsíce po operaci a pomocí škály pro hodnocení jizev pacienta a pozorovatele (the Patient and Observer Scar Assessment Scale – POSAS) 30 a 90 dnů po chirurgickém zákroku. K hodnocení negativního dopadu výsledků léčby na různé aspekty života pacienta byl použit dermatologický index kvality života (dermatology life quality index – DQLI). **Výsledky:** Šířka jizev byla u léčené skupiny 2× menší. Pacienti v PRP léčené skupině byli s výsledky léčby spokojenější a měli vyšší kvalitu života. Ošetřovaná skupina vykazovala ve všech časových bodech méně jizvení než kontrolní skupina 3 měsíce po operaci. **Závěr:** Použití PRP mělo výrazný příznivý terapeutický účinek v rámci ovlivnění estetických výsledků chirurgických zákroků.

Anaplastický velkobuněčný lymfom spojený s prsním implantátem – evoluce v průběhu desetiletí: citační analýza 50 nejcitovanějších článků

A. P. Kallarackal, I. Slaninka, N. Mrozková

Úvod: Anaplastický velkobuněčný lymfom spojený s prsním implantátem (breast implant-associated anaplastic large cell lymphoma – BIA-ALCL) je nedávno objevená malignita T buněk vznikající při použití silikonových prsních implantátů. Předpokládá se, že etiologie může být spojena s růstem bakterií a dlouhodobým zánětem. U postižené pacientky se obvykle objeví otok prsu v důsledku nahromadění periimplantátové tekutiny. V současné době je diagnostika prováděna pomocí ultrazvuku, biopsie a testování určitých biomarkerů. Další léčba spočívá v úplné chirurgické excizi a kapsulektomii s výměnou za implantáty s hladkým povrchem. Cílem této studie bylo identifikovat a představit 50 nejcitovanějších článků týkajících se oblasti BIA-ALCL. **Metody:** K identifikaci 325 článků týkajících se BIA-ALCL byl použit citační index Web of Science. Do této studie bylo zahrnuto 50 nejcitovanějších článků z nich. Byl evidován název, jméno autora, časopis a rok vydání, země a institut původu, úroveň důkazu (level of evidence – LoE), typ studie (klinická nebo základní) a téma studie (patofyziologie, onkologický management, diagnostika, kazuistiky a případy). **Výsledky:** Tato studie zahrnuje články od roku 1997 do roku 2018 s průměrnou citací 65,5. U většiny citovaných článků (36 %; n = 18) byly nalezeny kazuistiky, následovaly série případů (18 %; n = 9), systémové recenze (12 %; n = 6) a studie zaměřené na patofyziologii (16 %; n = 8), onkologický management (6 %; n = 3), databáze (6 %; n = 3), diagnostika (4 %; n = 2) a informovaný souhlas (2 %; n = 1). Články byly publikovány ve 30 časopisech a pocházely z 35 ústavů. Země původu většiny studií byly Spojené státy. Přestože žádný z článků nedosáhl úrovně důkazu 1, u většiny bylo zjištěno, že mají úroveň důkazu 4 (n = 11) nebo 5 (n = 19). Většina článků (n = 42) představovala klinický výzkum. **Závěr:** Podle této citační analýzy je velká část stávající literatury o BIA-ALCL s vysokým impaktem zaměřena na sledování onemocnění. Doufáme, že prostřednictvím této studie představíme jednoduchý vzdělávací nástroj, který umožní lépe ocenit výzkum v této relativně mladé oblasti.

Kostní invaze u orálního spinocelulárního karcinomu

D. Král, R. Pink, L. Šašková, J. Michálek, P. Tvrdý

Úvod: S ohledem na anatomické vztahy v dutině ústní může orální spinocelulární karcinom atakovat horní nebo dolní čelist. Podle systému TNM jsou nádory, které napadají kortikální kostí, klasifikovány jako T4a, stadium IVA. Invaze do kosti u orálního spinocelulárního karcinomu se nejčastěji vyskytuje u nádorů blízko kosti nebo u větších a pokročilejších nádorů. Je považována za nepříznivý prognostický faktor a často je diagnostickým a terapeutickým problémem. Destrukce kostní tkáně je zprostředkována aktivovanými osteoklasty, nikoli přímo karcinomem. Důležitou roli v osteoklastogenezi hrají proteiny ze skupiny receptorů faktoru nádorové nekrózy – RANK, RANKL a OPG. Podle histologického hlediska existují tři vzorce invaze kosti – erozivní, smíšený a infiltrační. Nejčastěji používanými zobrazovacími technikami při hodnocení kostní invaze orálním spinocelulárním karcinomem jsou CT a MRI. **Cíl:** Tento přehled je zaměřen na buněčné a molekulární mechanizmy, histologické vzorce a detekční metody kostní invaze způsobené orálním spinocelulárním karcinomem.

Trojrozměrná navigace v maxilofaciální chirurgii – způsob, jak minimalizovat chirurgický stres a zlepšit přesnost chirurgických zákroků u volného laloku z fibuly a u chirurgického zákroku při Eaglově syndromu

L. Czakó, M. Vavro, B. Dvoranová, M. Soviš, K. Šimko, A. Thurzo, B. Gális, F. Sándor

Úvod: Chirurgická navigace s technikami trojrozměrného (3D) tisku představuje dvě hlavní výhody: za prvé, z technického hlediska usnadňuje orientaci v cílových anatomických strukturách, což vede ke zlepšení přesnosti chirurgického zákroku. Navíc zkracuje dobu složitých chirurgických zákroků tím, že připravuje přesnou polohu přizpůsobených autologních štěpů pomocí fixačních zařízení. Za druhé, z klinického hlediska zkracuje dobu operace a také zmenšuje dopad chirurgického stresu na sousední tkáně. **Materiál a metody:** V této studii byly pomocí 3D navigace a plánování hodnoceny dva maxilofaciální postupy – resekce styloidního procesu v důsledku Eaglova syndromu a mikrovaskulární rekonstrukce mandibuly volným lalokem z fibuly. Všichni pacienti, kteří podstoupili tyto postupy, byli rozděleni do dvou skupin (s 3D navigací nebo bez ní). **Výsledky:** Ve skupině Eaglova syndromu nezávislý t-test ukázal významný rozdíl v operační době mezi skupinou 1 (M = 148; SD = 0) a skupinou 2 (M = 78; SD = 4,24; t (1) = 13,472; p = 0,047. Nebyl žádný významný rozdíl v délce pooperační hospitalizace (2 dny), který byl stejný ve všech skupinách pacientů. Ohledně rekonstrukce čelisti volným lalokem z fibuly, nezávislý t-test odhalil významný rozdíl v operačním čase s 3D tiskovými šablonami (M = 8:40:25; SD = 0:58:07) a bez nich (M = 10:43:15; SD = 3 :04:32); t (14) = 2,133; p = 0,051. Podobně nebyl žádný významný rozdíl mezi skupinami (skupina 1 M = 15,5; SD = 0,71; skupina 2 M = 13; SD = 1,63) v délce trvání pooperační hospitalizace; t (4) = 1,98; p = 0,119. **Závěr:** Stručně řečeno, zkrácení doby operace při Eaglově syndromu a při mikrovaskulární rekonstrukci dolní čelisti pomocí volného laloku z fibuly zmírňuje chirurgický stres na cílové tkáně, což umožňuje rychlejší hojení tkání a rychlejší zotavení.

ACTA CHIRURGIAE PLASTICAE

INTERNATIONAL JOURNAL OF PLASTIC SURGERY, MAXILLOFACIAL SURGERY, HAND SURGERY AND BURNS

- Founded 1959
- Published four times a year
- Peer-reviewed
- Original scientific papers
- Latest news and important information from the specialty
- Printed and online versions

Follow Acta chirurgiae plasticae online:
www.prolekare.cz/en/journals/acta-chirurgiae-plastiacae

Care Comm
we care...

ČSPCH

ČESKÁ LÉKAŘSKÁ SPOLEČNOST · J. E. PURKYNĚ ·

ACTA CHIRURGIAE PLASTICAE

Ministry of Culture of the Czech Republic Reg. No. MK ČR E4844. ISSN (print) 0001-5423, ISSN (online) 1805-4404.

Published by CareCom s.r.o., Klicperova 604/8, 150 00 Prague 5, Czech Republic.

Editing: Petra Polsen, e-mail: petra.polsen@carecomm.cz

Graphic design: Miroslav Chudík, e-mail: mirek.chudik@carecomm.cz

Issued: 4 times per year. Annual subscription: 870 CZK. Information on subscription: predplatne@carecomm.cz

Advertisement: Nikola Janková, phone: +420608848496, e-mail: niki.jankova@carecomm.cz

The manuscript and a cover letter may be sent in an electronic form to the following address: zdenek.dvorak@fnusa.cz. Printed papers are not paid; the authors receive one copy of the journal for free.

This issue is published on 27. 10. 2021