RESEARCH

ORIGINAL ARTICLE

Study of the Effect of Different Breast Implant Surfaces on Capsule Formation and Host Inflammatory Response in an Animal Model

Fabio Santanelli di Pompeo, MD, PhD; Michail Sorotos, MD, PhD; Rossella Canese, PhD; Mauro Valeri, PhD; Roberto Cirombella; Giorgia Scafetta; Guido Firmani, MD; and Arianna di Napoli, MD, PhD

Dr Santanelli di Pompeo is a full professor of plastic surgery, School of Medicine and Psychology, Sapienza University, Rome - Sant'Andrea Hospital, Rome, Italy. Dr Sorotos is an assistant professor of plastic surgery, Department of Neuroscience, Mental Health and Sense Organs (NESMOS), Sapienza University, Sant'Andrea Hospital, Rome, Italy. Dr Canese is a senior research scientist, Unit-Core Facilities, Superior Istitute of Health, Rome, Italy. Dr Valeri is the head of proceedings, Center for Animal Experimentation and Well-Being, Istituto Superiore di Sanità, Rome, Italy. Mr Cirombella and Ms Scafetta are laboratory technicians, Pathology Unit, Department of Clinical and Molecular Medicine, Sapienza University, Sant'Andrea Hospital, Rome, Italy. Dr Firmani is a plastic surgery resident, Department of Neuroscience, Mental Health and Sense Organs (NESMOS), Sapienza University, Sant'Andrea Hospital, Rome, Italy. Dr di Napoli is an associate professor of pathology, Pathology Unit, Department of Clinical and Molecular Medicine, Sapienza University, Sant'Andrea Hospital, Rome, Italy.

Corresponding Author: Dr Fabio Santanelli di Pompeo, Azienda Ospedaliera Sant'Andrea – U.O.D. Chirurgia Plastica, Via di Grottarossa 1035-1039, 00189, Rome, Italy.
E-mail: Fabio.santanelli@uniroma1.it; Instagram: @diepflap.it

Disclosures: Dr Santanelli di Pompeo would like to disclose that the NESMOS Department (Sapienza University, Sant'Andrea Hospital, Rome, Italy) with which they are affiliated has received research funds from Motiva (Houston, TX, USA), Establishment Labs (Alajuela, Costa Rica) in 2017, and from GC Aesthetics (Dublin, Ireland) in 2018 and 2020. The NESMOS Department has also received mini implants from Establishment Labs, GC Aesthetics, and Sebbin (Boissy l'Aillerie, France) for research purposes. Dr Santanelli di Pompeo is a paid consultant for BellaSeno GmbH (Leipzig, Germany), has received reimbursements for travel/lodgment expenses from ICEAG in 2015 and SCHEER-WG in 2019, 2020 and 2021, and is a member of Notified Body 0373, part of the Superior Institute of Health (Rome, Italy), which carries out CE Mark certification activities for the Italian Ministry of Health for the year 2021.

The other 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/or publication of this article.

[AQ: Please provide any academic degrees obtained for authors Roberto Cirombella and Giorgia Scafetta (for example, BS, MD, etc.).]

[AQ: In the disclosures, please provide the full names of ICEAG and SCHEER-WG, as well as the locations of the company headquarters (city, state, country, etc.).]

Abstract

Background: Breast implants are biomaterials eliciting a physiological and mandatory foreign body response.

Objectives: We designed an animal study to investigate the impact of different implant surfaces on the formation of the perirprosthetic capsule, the inflammatory response and the cellular composition.

Methods: We implanted 1 scaled-down version of breast implants by different manufactures on 70 female Sprague Dawley rats. Animals were divided into five groups of 14 animals. Group A received a smooth implant (Ra≈0.5μm) according to the ISO 14607-2018 classification, Group B smooth implant (Ra≈3.2μm), Group C smooth implant (Ra≈5μm), Group D macrotextured implant (Ra≈62μm) and Group E macrotextured implant (Ra≈75μm). At 60 days, all animals received a magnetic resonance imaging (MRI) and 35 animals were sacrificed and their capsules sent for histology (capsule thickness, inflammatory infiltrate) and immunohistochemistry analysis (cellular characterization). The remaining animals repeated the MRI at 120 days and were sacrificed following the same protocol.

Results: MRI showed a thinner capsule in the smooth implants (Group A,B,C) at 60 days ($p<0.001$) but not at 120 days ($p=0.039$), confirmed with histology both at 60 days ($p=0.005$) and 120 days ($p<0.001$). Smooth implants (Group A, B, C) presented a mild inflammatory response at 60 days that was maintained at 120 days and a high M2-Macrophage concentration (anti-inflammatory).

Conclusions: Our study confirms that smooth implants form a thinner capsule, inferior inflammatory infiltrate and a cellular composition that indicates a mild host inflammatory response. A new host inflammatory response classification is elaborated classifying breast implants into mild, moderate, and high.

Breast implants are widely used in plastic surgery both for aesthetic and reconstructive purposes. Although there are no biomaterials with comparable characteristics in terms of availability, adaptability and immunogenicity on the market, silicone remains a foreign body and as such, it induces a physiological and mandatory foreign body response.[1] A variety of inflammatory cells participate in the reaction against the inserted implant and the creation of the periprosthetic capsule.[2] Capsular contracture is the most common long-term complication after both cosmetic and reconstructive surgery, and it is classified into four degrees according to the Baker scale. Visible deformity, palpable hardness and progressive pain make capsular contracture clinically relevant in up to 30% of cosmetic surgery cases and in 73% reconstructive ones, especially in patients who have undergone radiotherapy treatment.[3-5] In 2011, the Food and Drug Administrations (FDA) issued an alert for women who had breast implants stating that although the risk was low, they were more likely than the general population to develop breast-implant associated anaplastic large cell lymphoma (BIA-ALCL).[6,7] In 2016, the WHO organization updated its classification including BIA-ALCL as a distinct pathology.[8,9] Its etiopathogenesis is unknown and therefore basic research and clinical studies are essential to understand its association with breast implants. Among the theories proposed the most acclaimed are a genetic predisposition, the effect of bacterial contamination, shell shedding of microparticles from the implant's surface, the effect of different shell surface characteristics, and a possible presence of toxins on the implant's surface.[10] All the different etiopathogenetic theories find chronic inflammation at the center of a mechanism potentially driving the transformation of T cells into lymphoma. Indeed, at molecular level, BIA-ALCL has been often characterized by constitutive activation of the JAK-STAT3 inflammatory pathway.[11-13] Breast implant surfaces are categorized based on different parameters such as pore size or diameter (μm), peak maximum height (μm), peak mean height (μm), kurtosis (sharpness of the profile), measured by the number and height of peaks (μm), skewness (profile symmetry), measured by the number and depth of valleys and peaks (μm), density (profile topography), measured by the average distance between morphological features (μm), roughness (μm). The most accepted classification at European Regulatory level is the ISO 14607:2018 classification which is based on the surface roughness (variations in height of the surface to a reference plane), dividing surfaces into smooth, micro, and macro.[14] Any implant with roughness below 10 μm is classified as a smooth. Implants with surface roughness of 10–50 μm are microtextured while implants with roughness >50 μm are

macrotextured. Nevertheless, according to the final opinion of the Scientific Committee on Health, Environmental and Emerging Risks (SCHEER), there is a need for an unambiguous clinically validated classification system for breast implants including more parameters than just "surface roughness".[15]

Since implants are designated to interact with human tissues, and inflammatory response has been hypothesized as a common trigger to most of implant complications, including BIA-ALCL, we believe that a new classification should be based on the type and degree of the inflammatory host response to different surfaces more than on the surface characteristics alone. To better understand the host/implant interaction, we designed an animal study to investigate the impact of different implant surfaces on the formation of the periprosthetic capsule and the cellular composition of the inflammatory response that characterize it.

METHODS

A research protocol was designed and presented for approval to the Ethics Committee of the Superior Institute of Health in Rome, Italy. The study was approved on June 20, 2018 (Protocol Number 453/2018-PR). Between January 2019 and January 2020, 70 female Sprague Dawley rats (Charles River Laboratories, Lecco, Italy) weighing 150-200g were randomly divided into five groups of 14 animals using block randomization. Each animal received one implant: Group A received an implant with a surface area of 0.5µm (smooth surface) according to the ISO 14607:2018 classification, Group B of 3.2µm (smooth surface), Group C of 5µm (smooth surface), Group D of 62µm (macrotextured surface) and Group E of 75µm (macrotextured surface). Devices used were scaled down versions (1.5 cm of diameter) of breast implants produced by different manufacturers. The animals were housed under a 12h light/dark cycle at room temperature (22 ± 1°C), with free access to water and rat chow. After 60 days, all animals received a magnetic resonance imaging (MRI) and 7 animals per group (35 animals in total) were sacrificed and the implant was removed together with the surrounding tissue to avoid contamination and alteration of the anatomy. The specimens were sent to the Pathology department for basic histology and immunohistochemistry analysis. The remaining animals, 7 per group for a total of 35 animals, were housed for another 60 days. At 120 days, since implantation, the remaining animals received a new MRI, were sacrificed, and their implants together with the surrounding tissue were sent to the Pathology department.

Surgical Technique

The animals were given inhalational general anesthesia (1.5-2.5% of isoflurane in 1L / min of O_2) and placed on the surgical table. The paravertebral region was shaved and prepared with betadine solution. The skin was incised at the level of the paravertebral region for a length of about 2 cm and the tissues were dissected under the panniculus carnosus muscle plane cranially towards the interscapular level. The mini implants were inserted and the skin was sutured with 4/0 nylon stitches. During explantation, the same preparation was performed, and the procedure included *en-bloc* removal of the breast implant and the surrounding tissues that were sent as fresh specimens to the pathology department for further analysis. The animals were sacrificed by placing them in a closed environment saturated with CO_2.

Magnetic Resonance Imaging

During the measurements, the animals received inhalational gas anesthesia (1.5-2.5% of isoflurane in 1L / min of O2), and their temperature was maintained at 37 ° C by means of a heated bed. MRI analyses were performed with a VARIAN INOVA SIS 200/183 spectrometer (Varian, Palo Alto, CA, USA) with a horizontal magnet for small animals, operating at 4.7 T. The measurement of the thickness of the capsule was performed on the axial plane. The most visceral height of this plane was chosen, and the measurements were made at the thickest portion of each quadrant and from the outer edge of the prosthesis towards the outer side of the skin. All measurements were performed by two blinded observers and expressed as mean values.

Histology and Immunohistochemistry

Periprosthetic capsules were formalin-fixed and paraffin-embedded. Two-micrometer sections were cut for both histology and immunohistochemical staining. Hematoxylin and eosin stained slides were used to evaluate the presence of synovial metaplasia, foreign body reaction, collagen fiber alignment and inflammatory infiltrate and to measure the thickness of the periprosthetic capsule and the vascular density. For each animal, the thickness of the capsule was calculated as the mean value of 20 measurements taken at the thinnest part and 20 measurements taken at the thickest part of the capsule using the ImageJ Measurement Tool (Version 1.46, National Institutes of Health, Bethesda, MD, USA). Immunohistochemistry was used to characterize and

quantify the cellular composition of the inflammatory infiltrate. Pax5 (Anti-Pax5 antibody [EPR3730(2)] ab109443, Abcam) was used to identify B-Cells, CD3 (Anti-CD3 antibody ab5690, Abcam) for T cells, Iba1 (Anti-Iba1 antibody [EPR16589] ab178847, Abcam) for macrophages, CD163 (anti-CD163 antibody [GTX42369], Labfor) for M2-type macrophages, and CD86 (anti—CD86 antibody [GTX34569], Labfor) for M1-type macrophages. The abundance of each inflammatory cell subset was calculated as mean value of the percentage of the positive cells for the relative marker on the total number of the cells counted in ten hotspots each with an area of 250 x 250μm. Differences among groups were evaluated using the Kruskal-Wallis H test. A p value of < 0.05 was considered statistically significant.

RESULTS

Capsule Thickness

MRI results (Table 1) showed a thinner capsule in the smooth implant groups (Group A,B,C) compared to the macrotextured implants (Group D, E), which was statistically significant at 60 days ($p<0.001$). At 120 days, only Group B had a statistically significant thinner capsule compared to the other smooth and macrotextured implants ($p<0.05$). When comparing MRI of the same group at 60 and 120 days, only group E had a statistically significant decrease in capsule thickness at 120days ($p=0.039$). Figure 1 presents MRI images of the capsules at 60 and 120 days.

Histology showed the presence of collagen fibers which were aligned in a mainly parallel fashion to the implant surface in most animals. Rats with macrotextured implants (Group D, E) presented a more compact alignment compared to those with smooth implants (Group A, B, C), although no significant difference was observed among the groups. Notably, the synovial metaplasia was completely absent in smooth implant groups, while constantly present in the capsules developed around the macrotextured implants. Similarly to MRI results, histology confirmed the presence of a thinner capsule in all smooth implant groups compared to the macrotextured implants that was statistically significant both at 60 days ($p=0.005$) and 120 days ($p<0.001$). Within each group we did not observe a statistically significant difference in capsule thickness at 60 and 120 days. Table 2 summarizes histological results. Figure 2 presents images of the capsules at 60 and 120 days.

Inflammatory Response

When evaluating the amount of inflammatory cellular infiltrate, we identified a significant difference among groups. Inflammatory response was determined primarily according to the percentage of M2 macrophages on the total number of the cells counted in ten hotspots for each specimen. The response was considered mild when over 50% of cells were M2 Macrophages, and high when the percentage was below 45%. A value between 45-49% was considered moderate. Smooth implant groups (Group A, B, C) presented a mild inflammatory response at 60 days that was maintained at 120 days. On the other hand, macrotextured implant groups (Group D, E) had a mild-to-moderate inflammatory response that in some cases was even high. The differences in the inflammatory response between the smooth and macrotextured implants was statistically significant both at 60 ($p<0.001$) and 120 days ($p=006$). Table 3 summarizes the results.

The inflammatory infiltrate was further characterized by immunohistochemistry to identify the presence of B cells, T cells, macrophages, and their subtypes M1 (pro-inflammatory) and M2 (anti-inflammatory). A low number of B cells was found in all groups both at 60 days and 120 days except for group C in which it was higher or increased at 120 days ($p<0.05$). T cells were more abundant compared to B cells, but equally low among all groups. Group B presented the lowest number of T cells both at 60 days ($p<0.05$) and 120 days ($p<0.05$). As expected, macrophages were the prevalent cell subtype in all groups. Capsules from macrotextured implants presented a lower percentage of macrophages compared to capsules from smooth implants. When analyzing the M1 vs M2 subpopulations, we observed a lower presence of M2 macrophages in the macrotextured implants capsules compared to the smooth ones. In all smooth implants groups (A, B, C), M2 macrophages represented more than 50% of the total macrophages while in the macrotextured groups (D, E) these were lower than 45%. Group B presented the highest number of M2 macrophages both at 60 and 120 days (Figures 3 and 4). Based on the above distinct profiles, we propose a "host inflammatory response" classification to divide implants into mild, moderate, and high according to M1/M2 ratio (Table 4).

DISCUSSION

Even though silicone is still considered an inert material, its presentation as a foreign body to the human immune system in the form of a breast implant elicits a host inflammatory response that relates to the development of a spectrum of complications such as seroma formation, capsular contracture, BIA-ALCL and a yet discussed but not confirmed clinical entity, called breast implant illness.[16-18] The safety of breast implants has always been a topic of debate and they have been studied both by means of animal models and in vitro.[19] Moreover, post-marketing studies have evaluated their clinical safety as well. Nevertheless, their technology has undergone substantial changes in the last 10 years, also including the development of new smooth surfaces and a market shift due to the recall from the market of certain macrotextured implants.[20,21] In our study, we included recently developed implants (<10years) in group B and group C to further enrich the body of literature regarding the behavior of VIth generation implants in an animal model. One of the most recent studies by Manav et al[22] in 2020 assessed capsular contracture around silicone implants following bacterial contamination, demonstrating that smooth implants formed a thinner capsule and had an inferior inflammatory infiltrate compared to textured and polyurethane (PU) implants, even in the presence of Staphylococcus epidermidis and with or without antibiotic treatment. Moreover, capsules developed around PU implants had a significantly higher ratio of M1, pro-inflammatory, macrophages. Similarly, in our study smooth implants capsules presented a higher percentage of anti-inflammatory M2 macrophages compared to textured implants. Analogous findings were observed by Bergmann et al in PU implants.[23]

Fisher et al[24] found that silicone implants with textured surfaces led to temporarily thicker but less dense fibrotic capsules compared to smooth surfaces. Although we agree with the authors that capsule thickness is not always connected with degree of capsular contracture, in our study smooth implants had thinner capsules both at 60 and 120 days both at MRI and histological evaluation. Katzel et al[25] assessed the role of radiotherapy confirming that irradiated implants have thicker capsules. Giot et al[26] presented their delamination theory in the development of the double-capsule phenomenon in macro-textured implants. Although we did not observe such complication, in both our macrotextured implants groups we were able to identify the synovial metaplasia, that is a bio-tribological interface adaptation mechanism to chronic stress, possibly connected with double capsule formation.[27,28]

Our study additionally confirms findings from the very well-designed study conducted by Doloff et al,[29] where the authors assessed the foreign body response and capsular fibrosis following the placement of either miniaturized or full-scale clinically approved breast implant, in animal models (30 mice of the C57BL/6 strain for up to 6 months, 30 New Zealand White rabbits for up to 1 year) and in 21 patients who received revisional surgery following long-term implantation ranging from 7 months to 11 years. Six different breast implant surface topographies were tested on mice and rabbits: traditional Smooth (Mentor Smooth Round), SmoothSilk/SilkSurface (Motiva), microtextured VelvetSurface (Motiva), microtexured Siltex Round (Mentor MemoryGel), microtextured Microcell (Allergan) and macrotextured Biocell Round (Allergan NATRELLE INSPIRA SoftTouch). Out of the capsules obtained from human specimen, 10 had received smooth devices and 11 a macrotextured Biocell implant, five of which were healthy while 6 had developed BIA-ALCL. Doloff et al. demonstrated that implants with an average roughness of 4 μm provoked the least amount of inflammation and foreign body response, which concurs with our results.

Our study is limited by the fact that only an animal model (the Sprague Dawley rat) was used, with an implantation of up to four months. However, our population of 70 specimens was higher. Additionally, five surface topographies were tested: 3 smooth and 2 macrotextured. The mini implants were donated directly by the companies and were not produced by us. The absence of microtextured and PU surfaces, is due to them not being offered by sponsoring companies, which is another limitation to our study. Despite the above mentioned limitations we attempted to extend our results into a classification system based on the host inflammatory reaction that, nevertheless, needs to be validated with more extensive studies both on animal models and human models. Finally, inflammatory response in our study has only been assessed by characterizing and quantifying the macrophage subpopulations found in our specimen. A more granular analysis of inflammation based on analysis of gene expression, transcriptomics, proteomics and cytokine expression should be implemented for more definitive results.

The surface of breast implants and their physical characteristics are widely used to classify them into various types. Other than the ISO classification mentioned above, Barr et al[30] measured the roughness area of various implants in 2017 and classified them into nano <5μm, meso <15μm, micro 15-70μm and macro >70μm. Atlan et al[31] used the surface area in 2018 to classify implants into smooth 80-100mm^2, micro 100-200mm^2, macro 200-300mm^2, and those

>300mm^2 were considered plus macro. In 2018, Jones et al[32] used the roughness and propensity for bacterial growth and classified implants into minimal <25µm, low 25-75µm, intermediate 75-150µm and high>150µm. None of these classification systems have been adopted by regulatory authorities thus far. Additionally, the terms "macro," "micro," "mid- texture," "nano," "aggressive," and "rough" have also been traditionally used in a relatively arbitrary fashion by implant manufacturing marketers to differentiate products.[33]

Besides Jones et al.'s classification which considers a specific not yet demonstrated etiology, all above-mentioned classifications are only based on physical properties missing any connection to the pathogenetic mechanism common to all complications associated with breast implants, *i.e.* the chronic inflammatory response. As such, we can assume that the higher the inflammatory response is the more are the complication potentially produced by a specific type of implant, and we believe that a breast implant classification based on the type and degree of inflammation and not just physical properties alone is worth implementing. Based on the results of our study, indicating that smooth implants capsules present a higher percentage of anti-inflammatory M2 macrophages compared to macrotextured ones, we elaborated a new *"host inflammatory response*" classification dividing breast implants accordingly into mild, moderate and high. Differently from all the other classifications based on physical properties, the one proposed by this translational research can be easily validated further in a clinical setting. Indeed, further animal and clinical studies will provide us with the knowledge needed to modulate this inflammatory response for improved biomaterial biocompatibility.[34,35]

CONCLUSION

Our study based on mini implants offered directly from the industries that produce them, further confirms that smooth implants compared to macrotextured implants (according to ISO 14607:2018 classification) form a thinner capsule, inferior inflammatory infiltrate and a cellular composition that indicates a mild host inflammatory response. A new host inflammatory response classification is elaborated classifying breast implants into mild, moderate and high.

Acknowledgements

The authors would like to thank the personnel in the names of Antonio Vitelli, Andrea Martinelli and Flavio Torriani, of the Superior Institute of Health, Rome, Italy, that were responsible for the housing and the well-being of the animals.

REFERENCES

1. Anderson JM, Rodriguez A, Chang DT. Foreign body reaction to biomaterials. Semin Immunol. 2008;20(2):86-100. doi:10.1016/j.smim.2007.11.004
2. Wick G, Backovic A, Rabensteiner E, Plank N, Schwentner C, Sgonc R. The immunology of fibrosis: innate and adaptive responses. Trends Immunol. 2010;31(3):110-119. doi:10.1016/j.it.2009.12.001
3. Handel N, Cordray T, Gutierrez J, Jensen JA. A long-term study of outcomes, complications, and patient satisfaction with breast implants. Plast Reconstr Surg. 2006;117(3):757-772. doi:10.1097/01.prs.0000201457.00772.1d
4. Araco A, Caruso R, Araco F, Overton J, Gravante G. Capsular contractures: a systematic review. Plast Reconstr Surg. 2009;124(6):1808-1819. doi:10.1097/PRS.0b013e3181bf7f26
5. Rosato RM, Dowden RV. Radiation therapy as a cause of capsular contracture. Ann Plast Surg. 1994;32(4):342-345. doi:10.1097/00000637-199404000-00002
6. Center for Devices and Radiological Health (2018) Update on the safety of silicone gel-filled breast implants - exec sum, U.S. Food and Drug Administration. FDA. Available at: https://www.fda.gov/medical-devices/breast-implants/update-safety-silicone-gel-filled-breast-implants-2011-executive-summary (Accessed: October 31, 2022).
7. Santanelli di Pompeo F, Sorotos M, Clemens MW, Firmani G; European Association of Plastic Surgeons (EURAPS) Committee on Device Safety and Development. Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL): Review of Epidemiology and Prevalence Assessment in Europe. Aesthet Surg J. 2021;41(9):1014-1025. doi:10.1093/asj/sjaa285
8. 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. doi:10.1182/blood-2016-01-643569

9. di Pompeo FS, Paolini G, Firmani G, Sorotos M. History of breast implants: Back to the future. JPRAS Open. 2022;32:166-177. Published 2022 Mar 11. doi:10.1016/j.jpra.2022.02.004
10. Scientific Committee on Health, Environmental and emerging risks (SCHEER) (2021) Final opinion on the safety of breast implants in relation to anaplastic large cell lymphoma. Available at: https://health.ec.europa.eu/scientific-committees/scientific-committee-health-environmental-and-emerging-risks-scheer_en (Accessed: October 31, 2022).
11. Di Napoli A, De Cecco L, Piccaluga PP, et al. Transcriptional analysis distinguishes breast implant-associated anaplastic large cell lymphoma from other peripheral T-cell lymphomas. Mod Pathol. 2019;32(2):216-230. doi:10.1038/s41379-018-0130-7
12. 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. doi:10.1111/bjh.14431
13. DeCoster RC, Clemens MW, Di Napoli A, et al. Cellular and Molecular Mechanisms of Breast Implant-Associated Anaplastic Large Cell Lymphoma. Plast Reconstr Surg. 2021;147(1):30e-41e. doi:10.1097/PRS.0000000000007423
14. International Organization for Standardization (2018) ISO 14607:2018(en) Non-active surgical implants — Mammary implants — Particular requirements. Available at: https://inen.isolutions.iso.org/obp/ui#!iso:std:iso:14607:ed-3:v2:en (Accessed: October 31, 2022).
15. De Jong WH, Panagiotakos D, Proykova A, et al. Final opinion on the safety of breast implants in relation to anaplastic large cell lymphoma: Report of the scientific committee on health, emerging and environmental risks (SCHEER). Regul Toxicol Pharmacol. 2021;125:104982. doi:10.1016/j.yrtph.2021.104982
16. Munhoz AM, Clemens MW, Nahabedian MY. Breast Implant Surfaces and Their Impact on Current Practices: Where We Are Now and Where Are We Going?. Plast Reconstr Surg Glob Open. 2019;7(10):e2466. Published 2019 Oct 15. doi:10.1097/GOX.0000000000002466

17. Shauly O, Gould DJ, Patel KM. Microtexture and the Cell/Biomaterial Interface: A Systematic Review and Meta-Analysis of Capsular Contracture and Prosthetic Breast Implants. Aesthet Surg J. 2019;39(6):603-614. doi:10.1093/asj/sjy178
18. Magnusson MR, Cooter RD, Rakhorst H, McGuire PA, Adams WP Jr, Deva AK. Breast Implant Illness: A Way Forward. Plast Reconstr Surg. 2019;143(3S A Review of Breast Implant-Associated Anaplastic Large Cell Lymphoma):74S-81S. doi:10.1097/PRS.0000000000005573
19. Rohrich RJ, Kaplan J, Dayan E. Silicone Implant Illness: Science versus Myth?. Plast Reconstr Surg. 2019;144(1):98-109. doi:10.1097/PRS.0000000000005710
20. Hong P, Kim SS, Jeong C, et al. Four-Year Interim Results of the Safety of Augmentation Mammaplasty Using the Motiva Ergonomix™ Round SilkSurface: A Multicenter, Retrospective Study. Aesthetic Plast Surg. 2021;45(3):895-903. doi:10.1007/s00266-021-02152-3
21. Ramos-Gallardo G, Vélez-Benítez E, Cuenca-Pardo J, et al. What is the Process for Breast Implant Manufacturing? Inside Eight Breast Implant Factories. Aesthetic Plast Surg. 2020;44(6):2063-2074. doi:10.1007/s00266-020-01844-6
22. Manav S, Ayhan MS, Deniz E, et al. Capsular contracture around silicone miniimplants following bacterial contamination: an in vivo comparative experimental study between textured and polyurethane implants [published correction appears in J Plast Reconstr Aesthet Surg. 2020 Dec;73(12):2261]. J Plast Reconstr Aesthet Surg. 2020;73(9):1747-1757. doi:10.1016/j.bjps.2020.02.049
23. Bergmann PA, Tamouridis G, Lohmeyer JA, et al. The effect of a bacterial contamination on the formation of capsular contracture with polyurethane breast implants in comparison with textured silicone implants: an animal study. J Plast Reconstr Aesthet Surg. 2014;67(10):1364-1370. doi:10.1016/j.bjps.2014.05.040
24. Fischer S, Hirche C, Reichenberger MA, et al. Silicone Implants with Smooth Surfaces Induce Thinner but Denser Fibrotic Capsules Compared to Those with Textured Surfaces in a Rodent Model. PLoS One. 2015;10(7):e0132131. Published 2015 Jul 7. doi:10.1371/journal.pone.0132131

25. Katzel EB, Koltz PF, Tierney R, et al. A novel animal model for studying silicone gel-related capsular contracture. Plast Reconstr Surg. 2010;126(5):1483-1491. doi:10.1097/PRS.0b013e3181ef8b8e
26. Giot JP, Paek LS, Nizard N, et al. The double capsules in macro-textured breast implants. Biomaterials. 2015;67:65-72. doi:10.1016/j.biomaterials.2015.06.010
27. Efanov JI, Giot JP, Fernandez J, Danino MA. Breast-implant texturing associated with delamination of capsular layers: A histological analysis of the double capsule phenomenon. Ann Chir Plast Esthet. 2017;62(3):196-201. doi:10.1016/j.anplas.2017.02.001
28. Hall-Findlay EJ. Breast implant complication review: double capsules and late seromas. Plast Reconstr Surg. 2011;127(1):56-66. doi:10.1097/PRS.0b013e3181fad34d
29. Doloff JC, Veiseh O, de Mezerville R, et al. The surface topography of silicone breast implants mediates the foreign body response in mice, rabbits and humans. Nat Biomed Eng. 2021;5(10):1115-1130. doi:10.1038/s41551-021-00739-4
30. Barr S, Hill EW, Bayat A. Functional biocompatibility testing of silicone breast implants and a novel classification system based on surface roughness. Journal of the Mechanical Behavior of Biomedical Materials. 2017;75:75-81. doi:10.1016/j.jmbbm.2017.06.030
31. Atlan M, Nuti G, Wang H, Decker S, Perry T. Breast implant surface texture impacts host tissue response. J Mech Behav Biomed Mater. 2018 Dec;88:377-385. doi: 10.1016/j.jmbbm.2018.08.035.
32. Jones P, Mempin M, Hu H, Chowdhury D, Foley M, Cooter R, Adams WP Jr, Vickery K, Deva AK. The Functional Influence of Breast Implant Outer Shell Morphology on Bacterial Attachment and Growth. Plast Reconstr Surg. 2018 Oct;142(4):837-849.
33. Santanelli di Pompeo F, Clemens MW, Atlan M, et al. 2022 Practice Recommendation Updates From the World Consensus Conference on BIA-ALCL. Aesthet Surg J. 2022;42(11):1262-1278. doi:10.1093/asj/sjac133
34. Doloff JC, Veiseh O, Vegas AJ, et al. Colony stimulating factor-1 receptor is a central component of the foreign body response to biomaterial implants in rodents and non-human primates. Nat Mater. 2017;16(6):671-680. doi:10.1038/nmat4866

35. Farah S, Doloff JC, Müller P, et al. Long-term implant fibrosis prevention in rodents and non-human primates using crystallized drug formulations. Nat Mater. 2019;18(8):892-904. doi:10.1038/s41563-019-0377-5

Figure Legend

Figure 1. MRI Imaging of the periprosthetic capsules at 60 days top row: a) Group A smooth implant (Ra≈0.5µm), b) Group B smooth implant (Ra≈3.2µm), c) Group C smooth implant (Ra≈5µm), d) Group D macrotextured implant (Ra≈62µm) and e) Group E macrotextured implant (Ra≈75µm). MRI Imaging of the periprosthetic capsules at 120 days bottom row: f) Group A smooth implant (Ra≈0.5µm), g) Group B smooth implant (Ra≈3.2µm), h) Group C smooth implant (Ra≈5µm), i) Group D macrotextured implant (Ra≈62µm) and j) Group E macrotextured implant (Ra≈75µm).

Figure 2. Histology H&E staining 10x of the periprosthetic capsules at 60 days top row: a) Group A smooth implant (Ra≈0.5µm), b) Group B smooth implant (Ra≈3.2µm), c) Group C smooth implant (Ra≈5µm), d) Group D macrotextured implant (Ra≈62µm) and e) Group E macrotextured implant (Ra≈75µm). Histology H&E staining 10x of the periprosthetic capsules at 120 days bottom row: f) Group A smooth implant (Ra≈0.5µm), g) Group B smooth implant (Ra≈3.2µm), h) Group C smooth implant (Ra≈5µm), i) Group D macrotextured implant (Ra≈62µm) and j) Group E macrotextured implant (Ra≈75µm)

Figure 3. Characterization of the cellular infiltrate at 60 days. Low number of B cells and high number of T cells. Low M2 macrophages concentration in the macrotextured groups.

Figure 4. Characterization of the cellular infiltrate at 120 days. Low number of B cells and high number of T cells. Low M2 macrophages concentration in the macrotextured groups.

Table 1. MRI – Capsule Thickness Measurements

	Mean Capsule Thickness (µm)		Kruskall Wallis H ($p < 0.05$)
	60gg	120gg	
Group (Ra=0.5 µm) Smooth Implant	0.145	0.142	p=0.795
Group (Ra=3.2 µm) Smooth Implant	0.113	0.126	p=0.726
Group (Ra=5 µm) Smooth Implant	0.137	0.147	p=0.545
Group (Ra=62 µm) Macrotextured Implant	0.195	0.154	p=0.140
Group (Ra=>75 µm) Macrotextured Implant	0.186	0.149	p=0.039
Kruskall Wallis H ($p < 0.05$)	p<0.001	p=0.980	

Table 2. Histology – Capsule Thickness Measurements

	Mean Capsule Thickness (µm)		Kruskall Wallis H ($p < 0.05$)
	60gg	120gg	
Group (Ra=0.5 µm) Smooth Implant	0.214	0.220	p=0.844
Group (Ra=3.2 µm) Smooth Implant	0.280	0.213	p=0.118
Group (Ra=5 µm) Smooth Implant	0.221	0.241	p=0.758
Group (Ra=62 µm) Macrotextured Implant	0.320	0.407	p=0.071
Group (Ra=>75 µm) Macrotextured Implant	0.406	0.454	p=0.468
Kruskall Wallis H ($p < 0.05$)	P=0.005	p<0.001	

Table 3. Histology – Inflammatory Infiltrate (Mild, Moderate, High)

	Inflammatory Infiltrate		Kruskall Wallis H (p < 0.05)
	60gg	120gg	
Group (Ra=0.5 μm) Smooth Implant	Mild (100%)	Mild (100%)	p=1.000
Group (Ra=3.2 μm) Smooth Implant	Mild (100%)	Mild (100%)	p=1.000
Group (Ra=5 μm) Smooth Implant	Mild (100%)	Mild (100%)	p=1.000
Group (Ra=62 μm) Macrotextured Implant	Mild (28.6%) Moderate (71.4%)	Mild (57.1%) Moderate (42.9%)	P=0.298
Group (Ra=>75 μm) Macrotextured Implant	Mild (85.7%) Moderate (14.3%)	Mild (28.6%) Moderate (42.9%) High (28.6%)	p=0.708
Kruskall Wallis H (p < 0,05)	P<0.001	P=0.006	

Table 4. Santanelli di Pompeo Et Al Host inflammatory Response Classification

Classification			
ISO (14607:2018)	Smooth Average Surface Roughness <10μm	Micro Average Surface Roughness 10-50μm	Macro Average Surface Roughness >50μm
Santanelli di Pompeo et al Host Inflammatory Response	Mild M2 Macrophages % >50%	Moderate M2 Macrophages % 45-49%	High M2 Macrophages % <45%

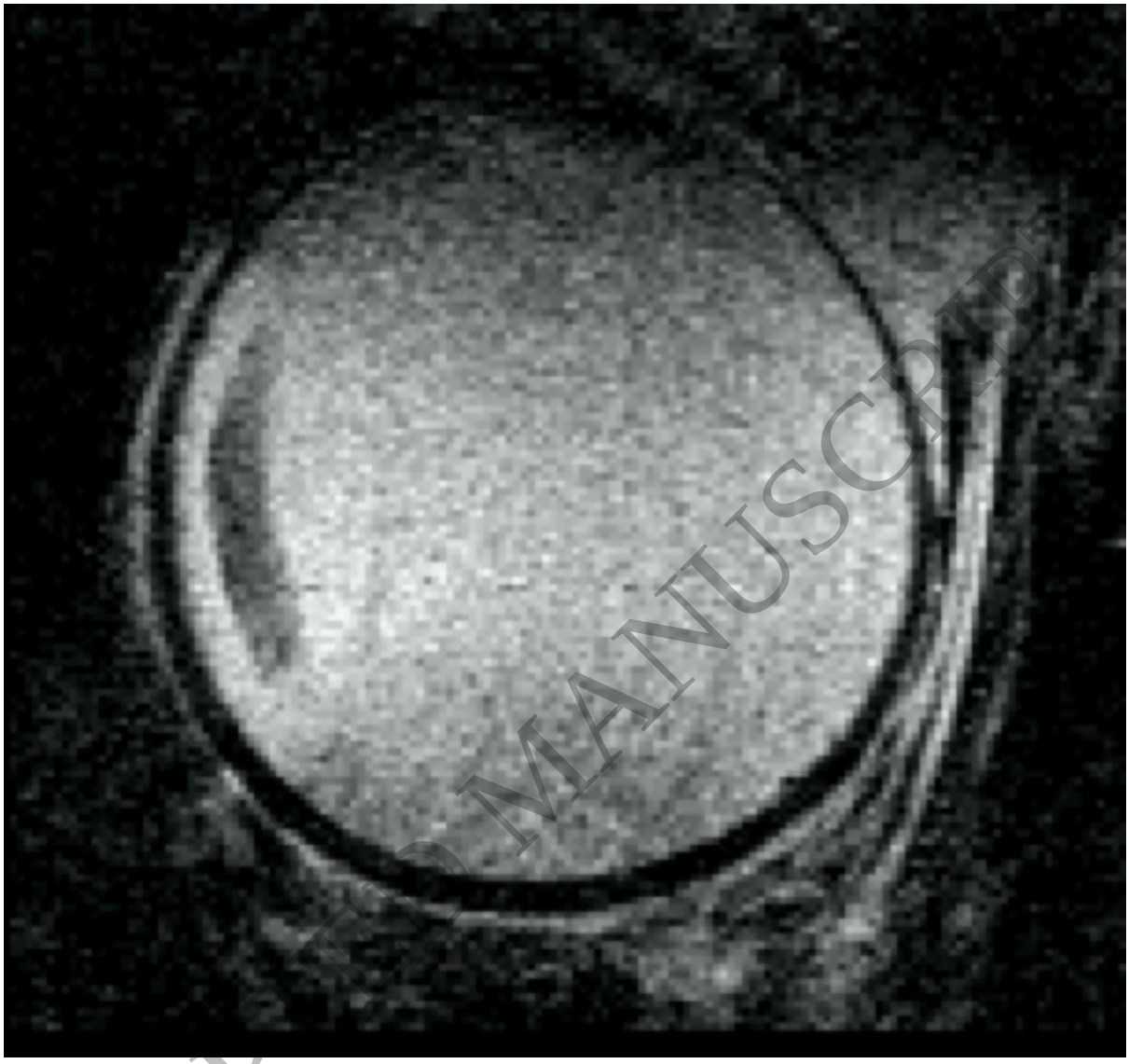

Figure 1A
159x149 mm (.33 x DPI)

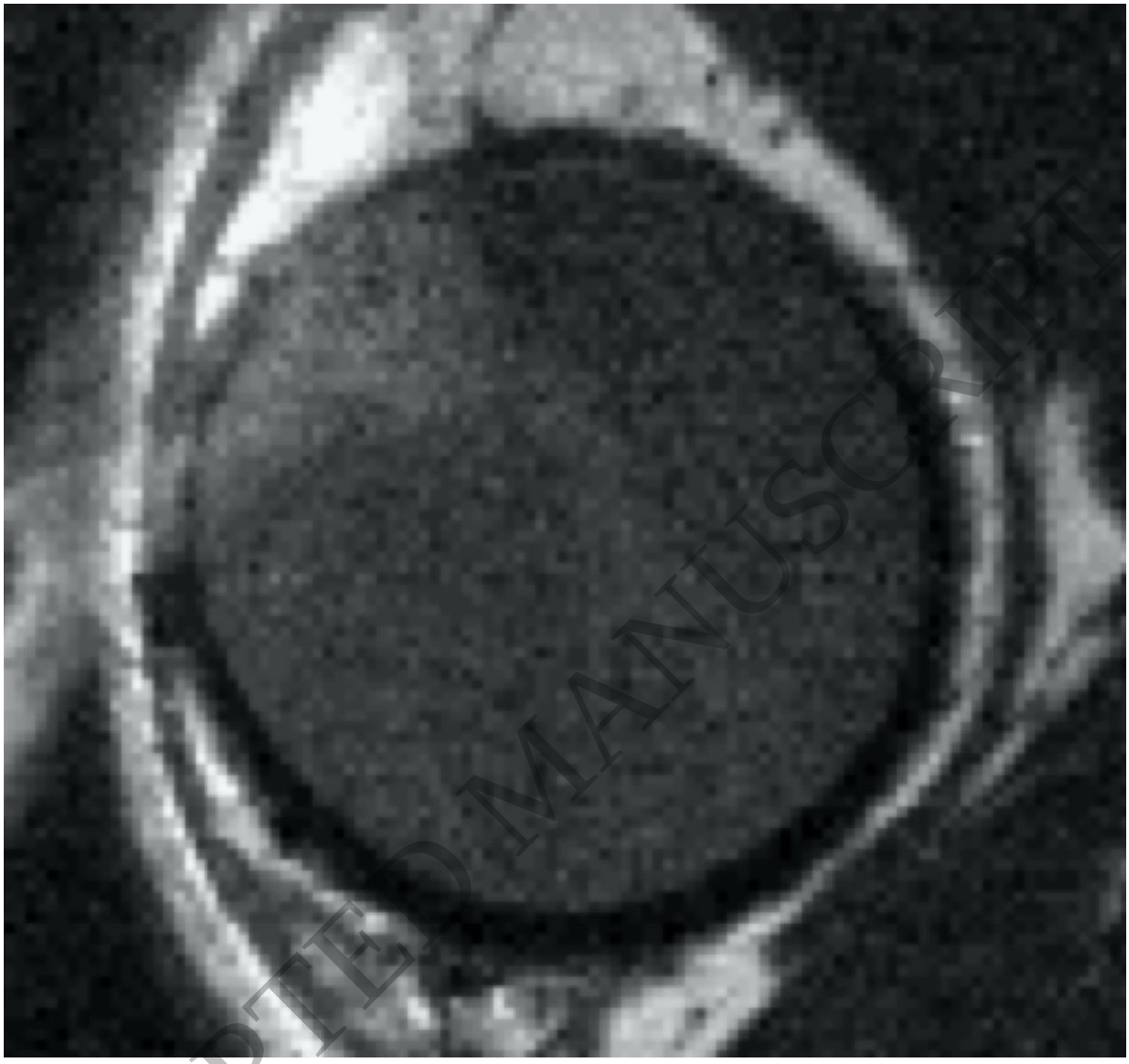

Figure 1B
159x149 mm (.33 x DPI)

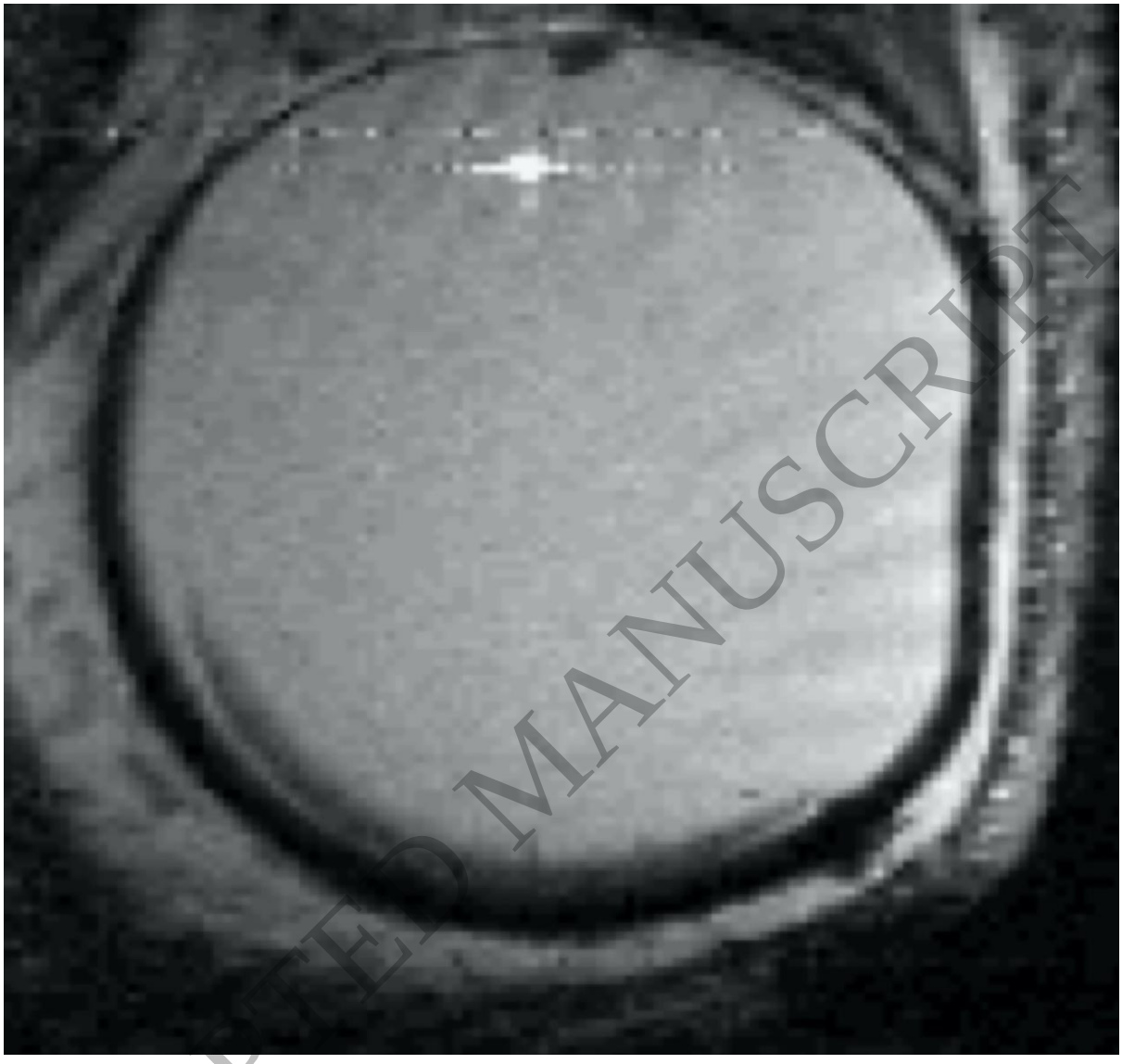

Figure 1C
159x150 mm (.33 x DPI)

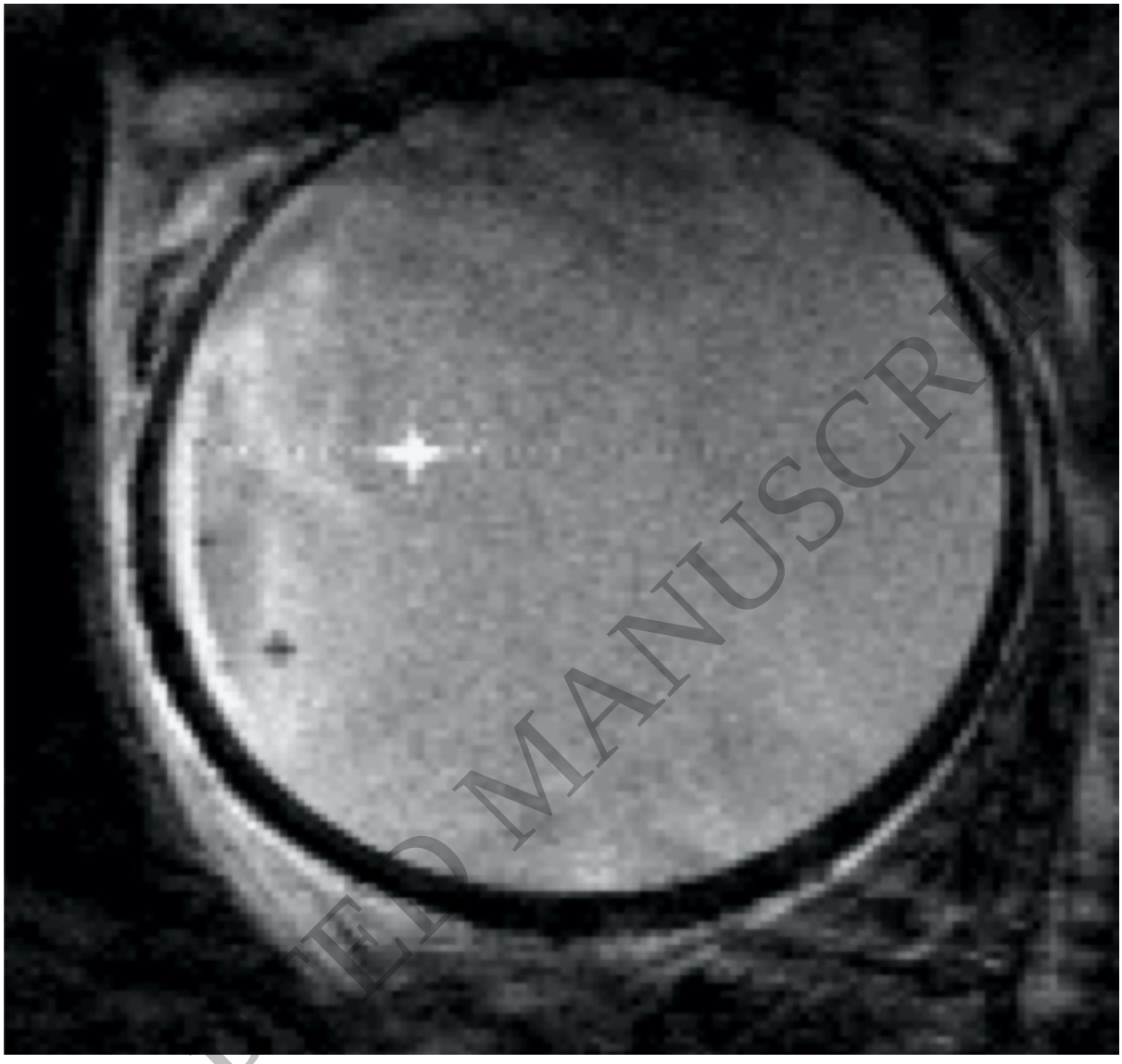

Figure 1D
159x150 mm (.33 x DPI)

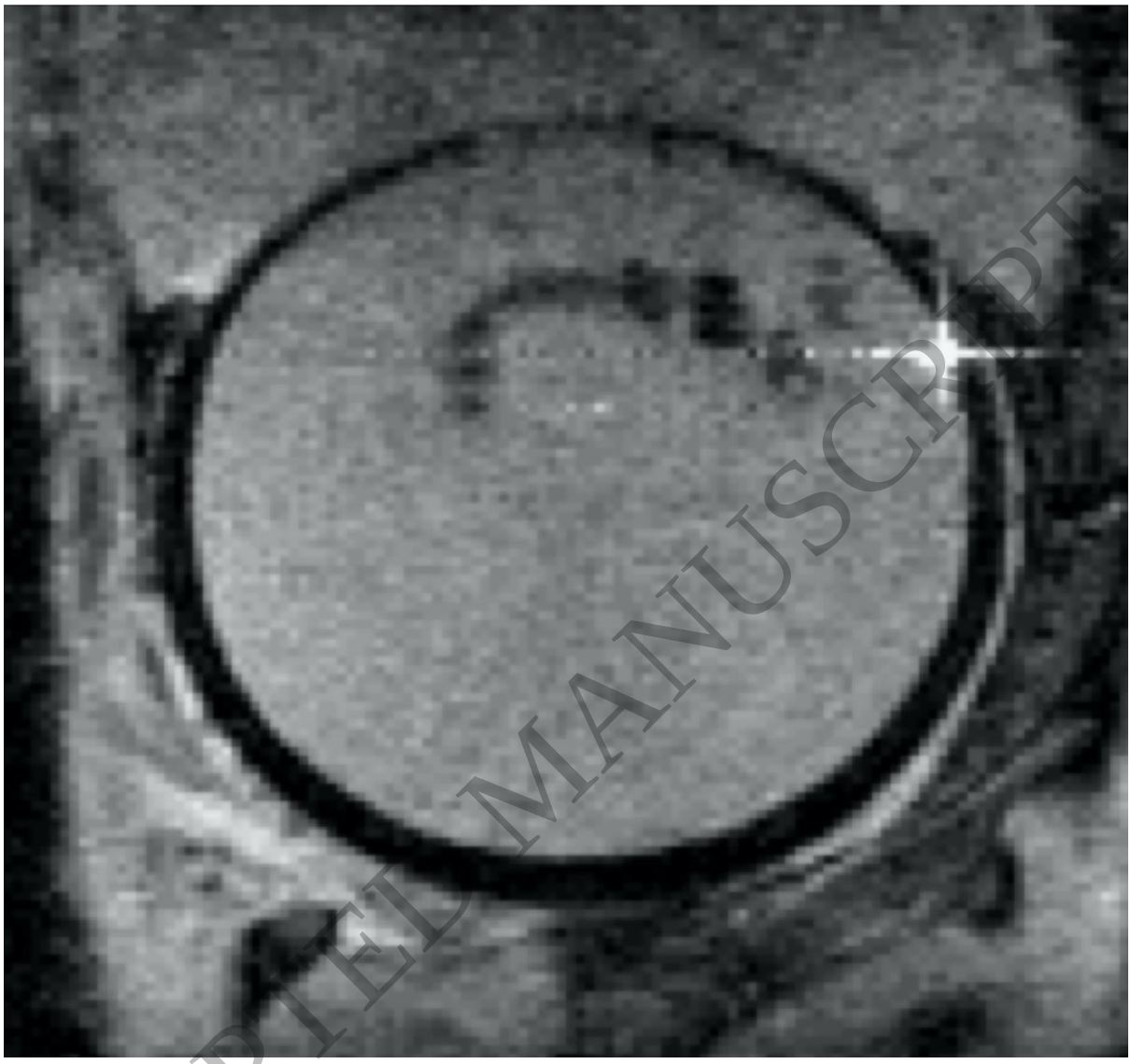

Figure 1E
159x149 mm (.33 x DPI)

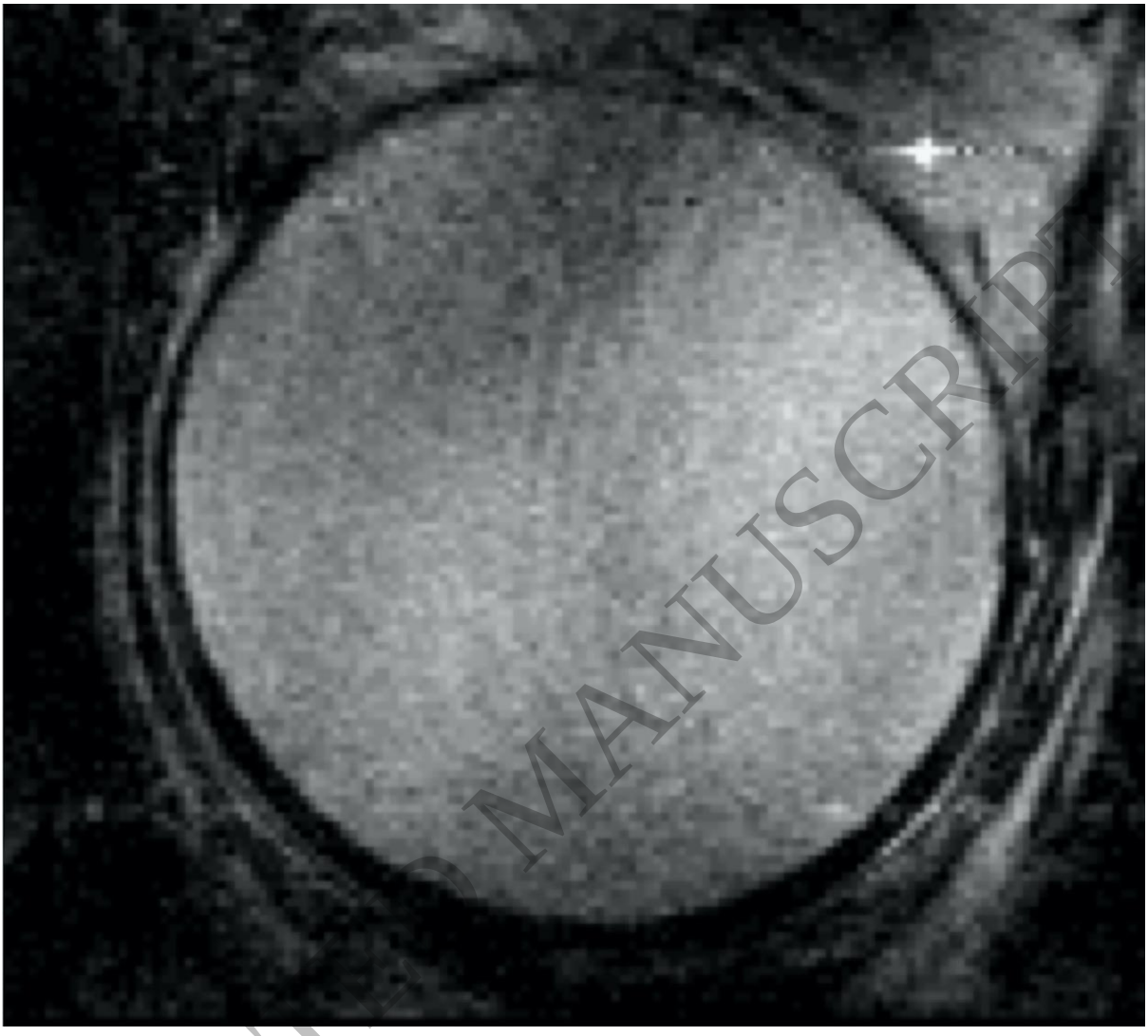

Figure 1F
159x142 mm (.33 x DPI)

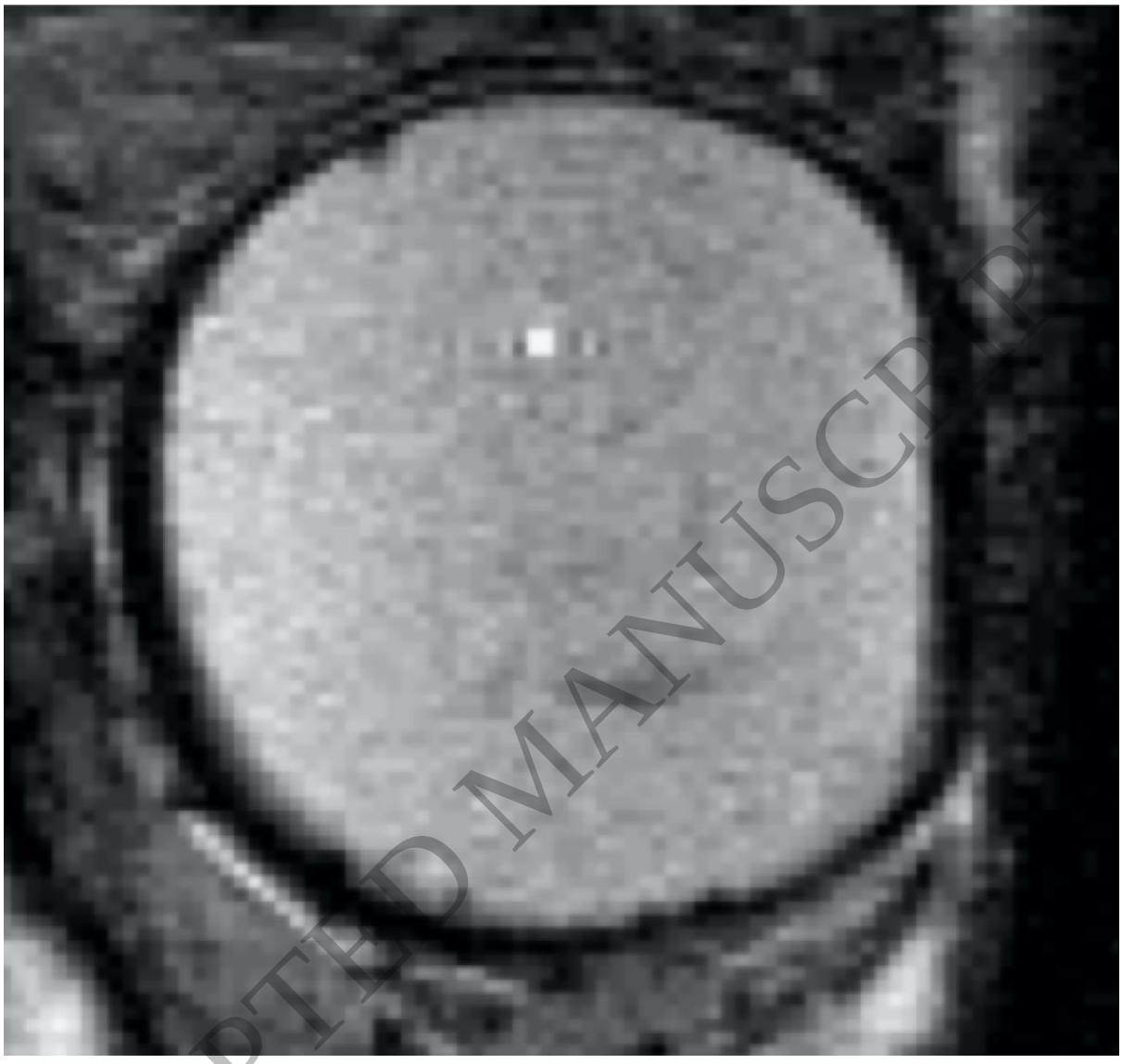

Figure 1G
159x150 mm (.33 x DPI)

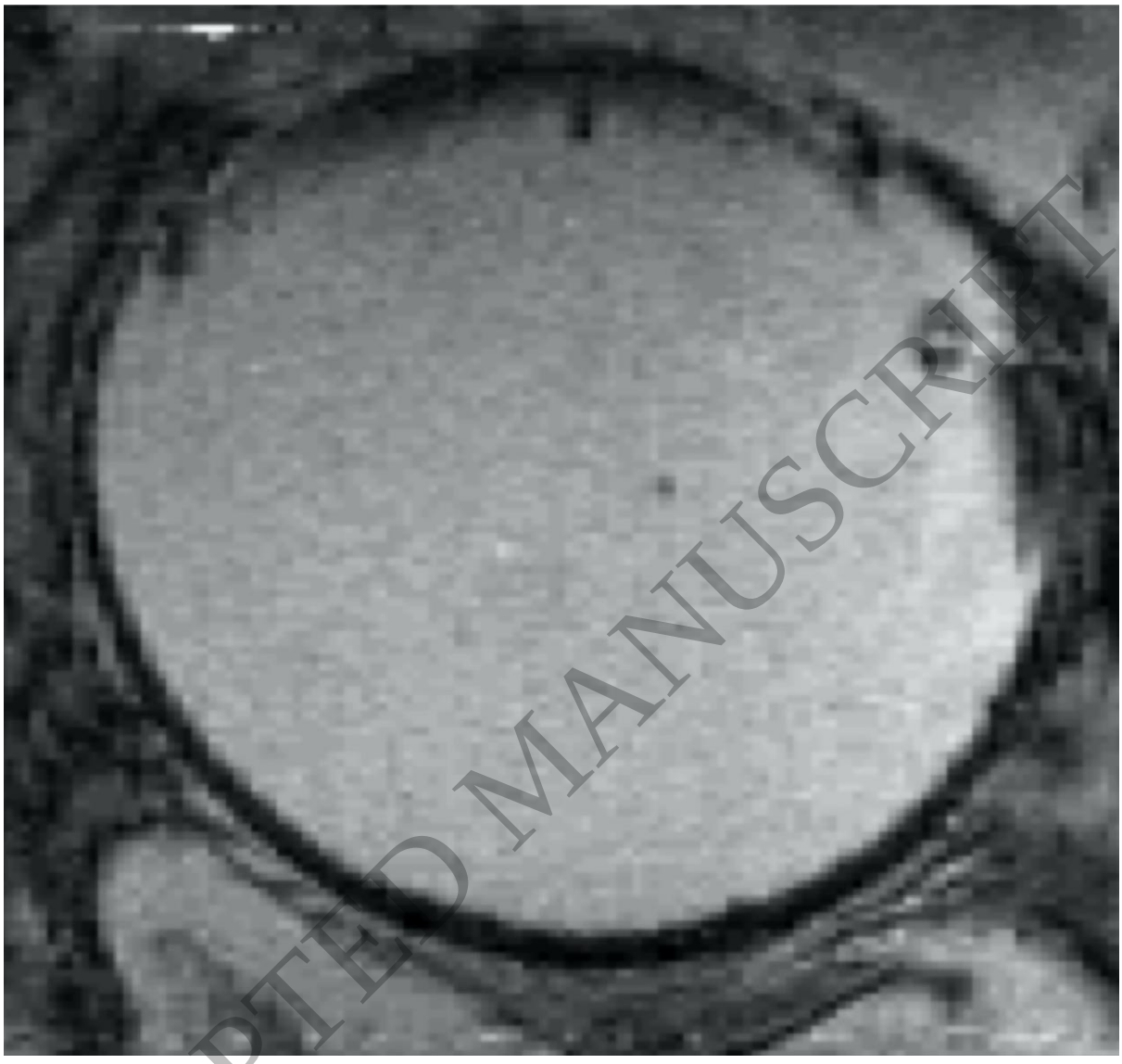

Figure 1H
159x150 mm (.33 x DPI)

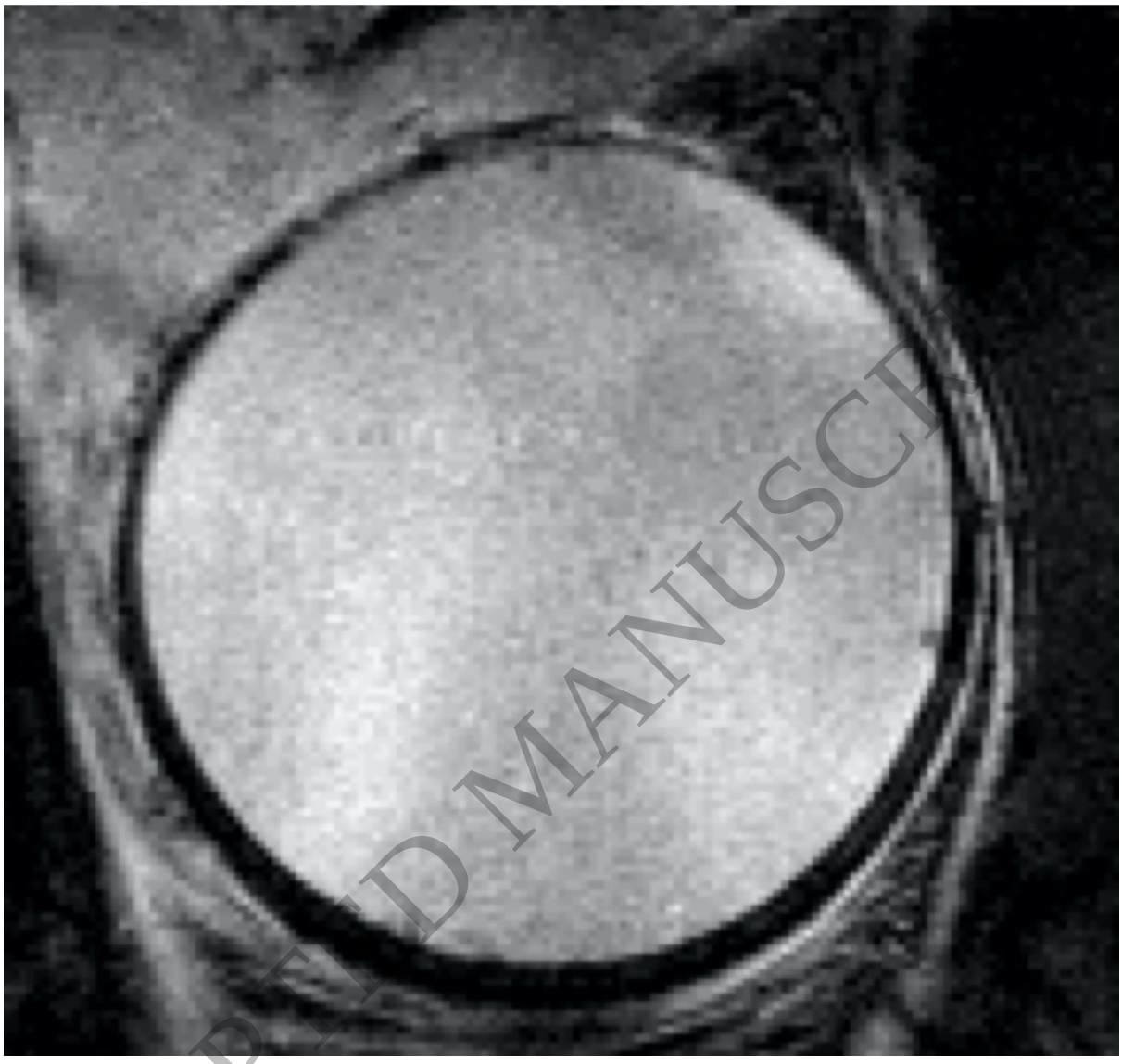

Figure 1I
159x150 mm (.33 x DPI)

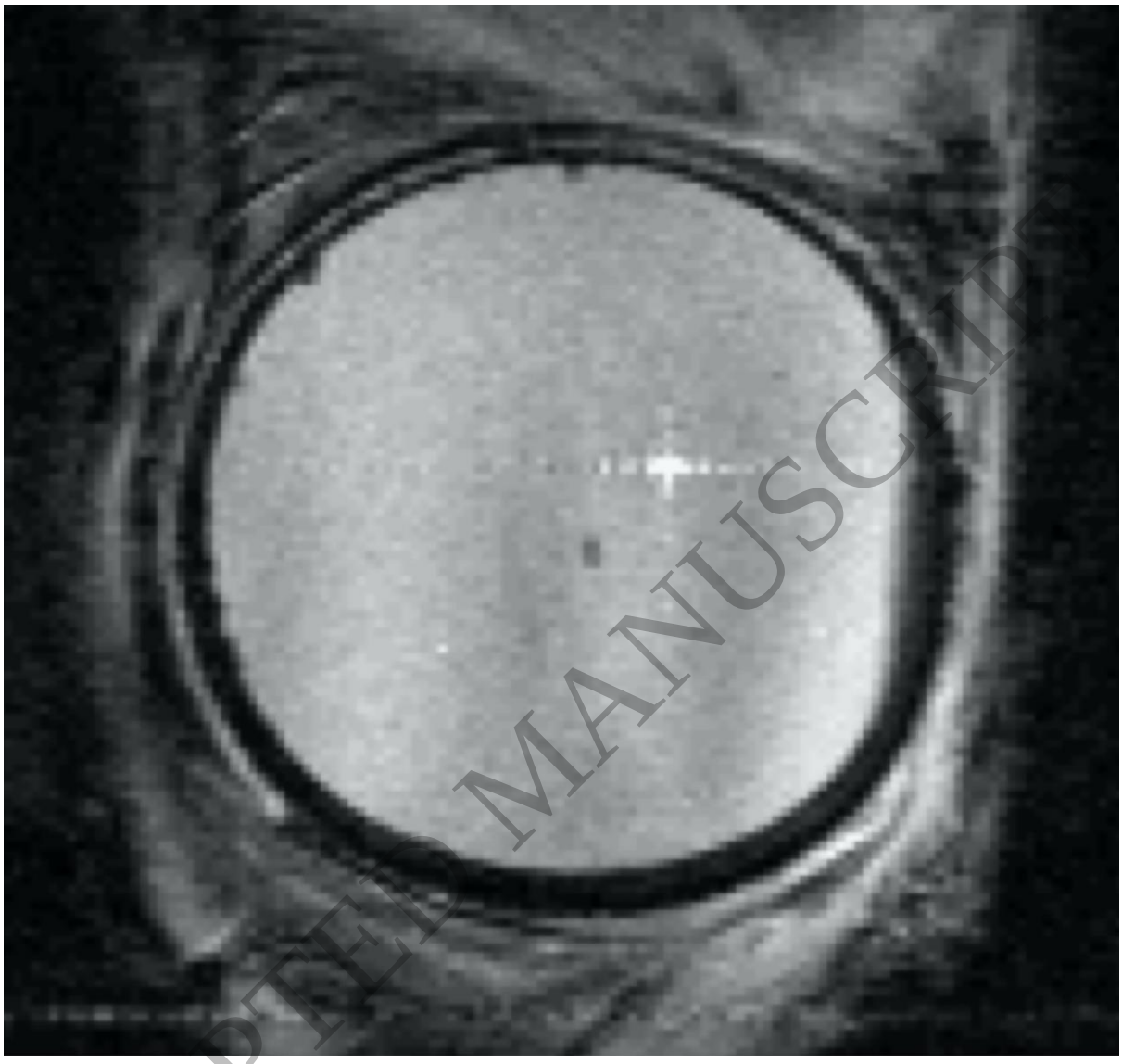

Figure 1J
159x150 mm (.33 x DPI)

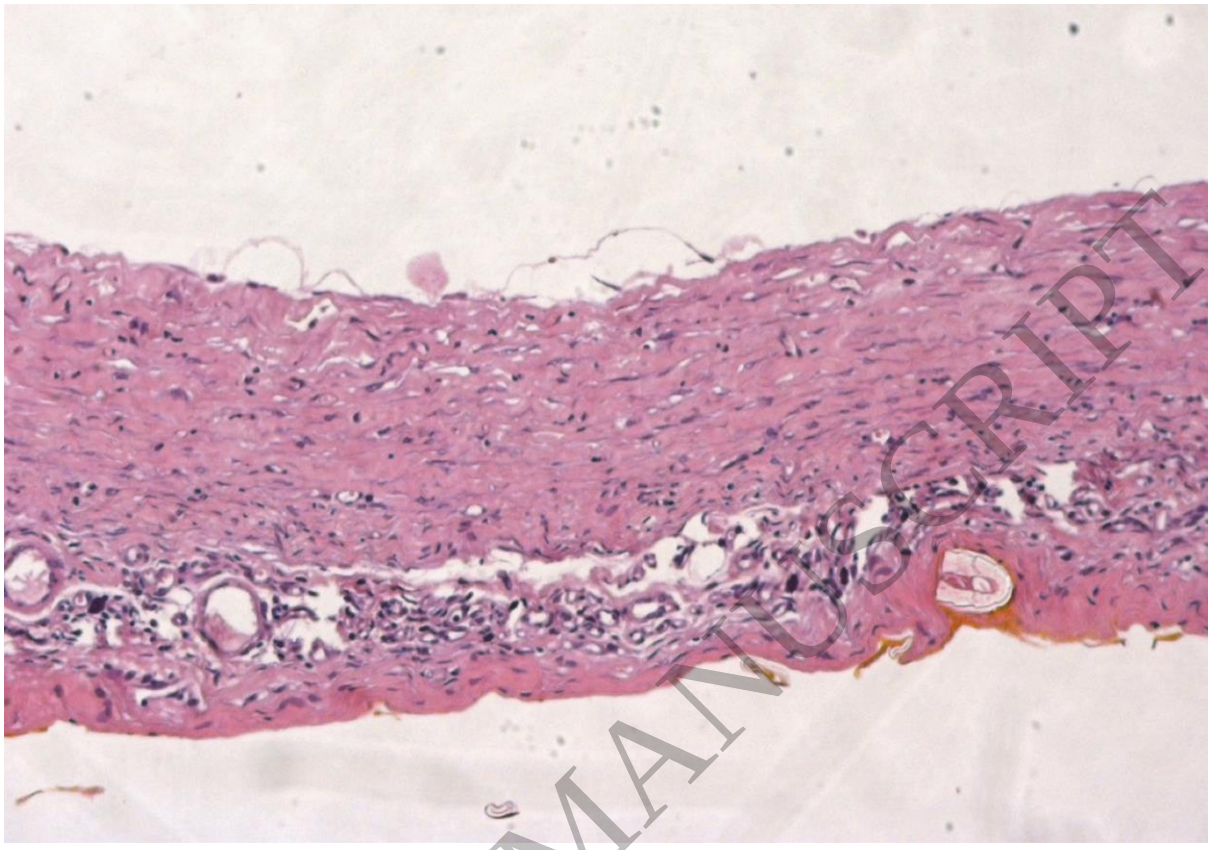

Figure 2A
159x111 mm (.33 x DPI)

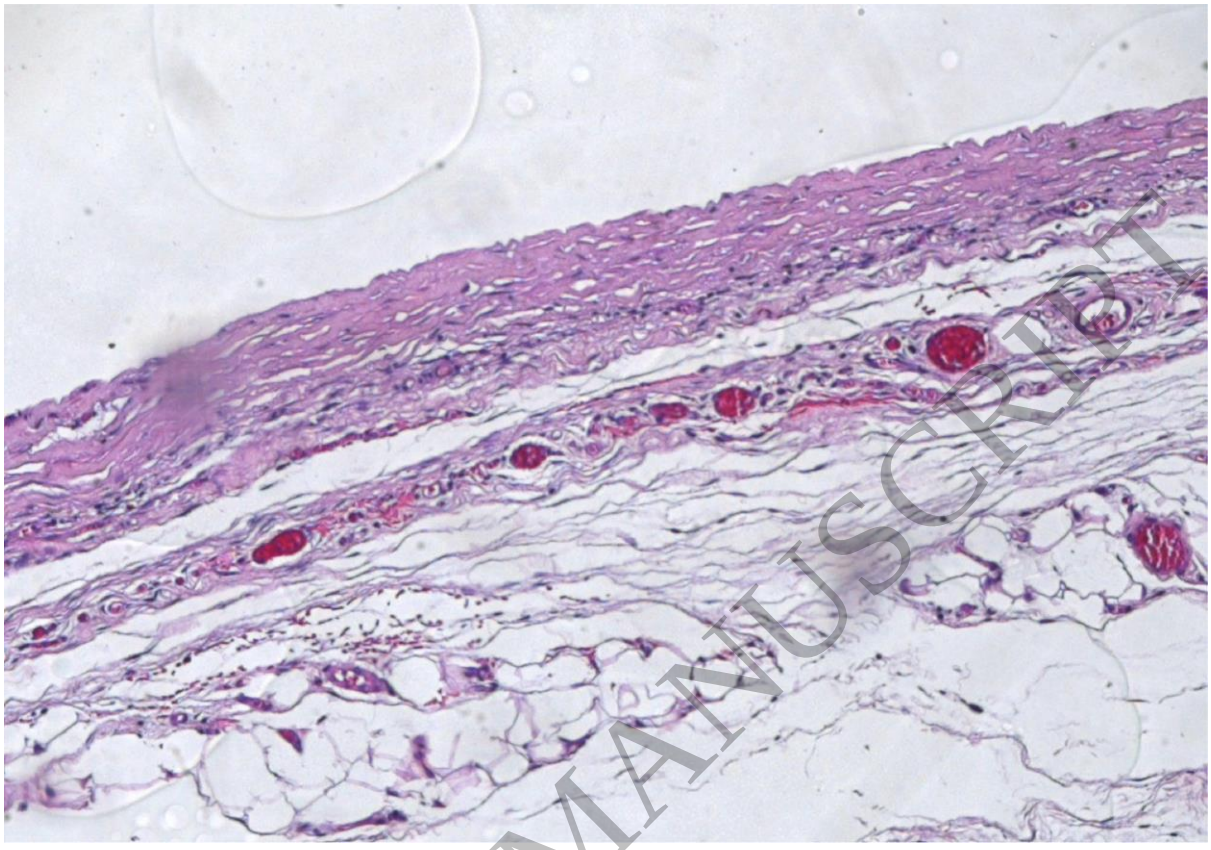

Figure 2B
159x111 mm (.33 x DPI)

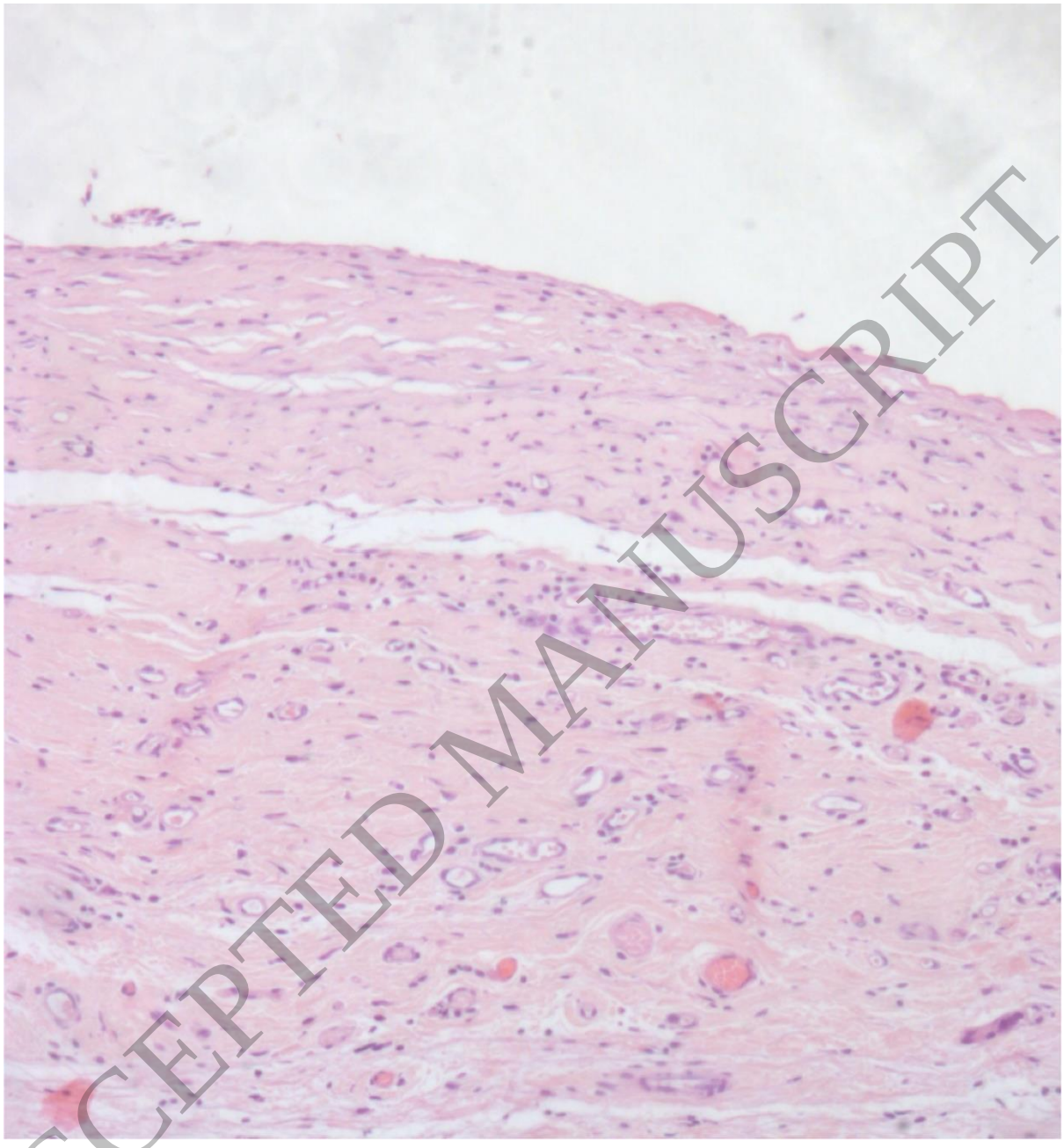

Figure 2C
159x171 mm (.33 x DPI)

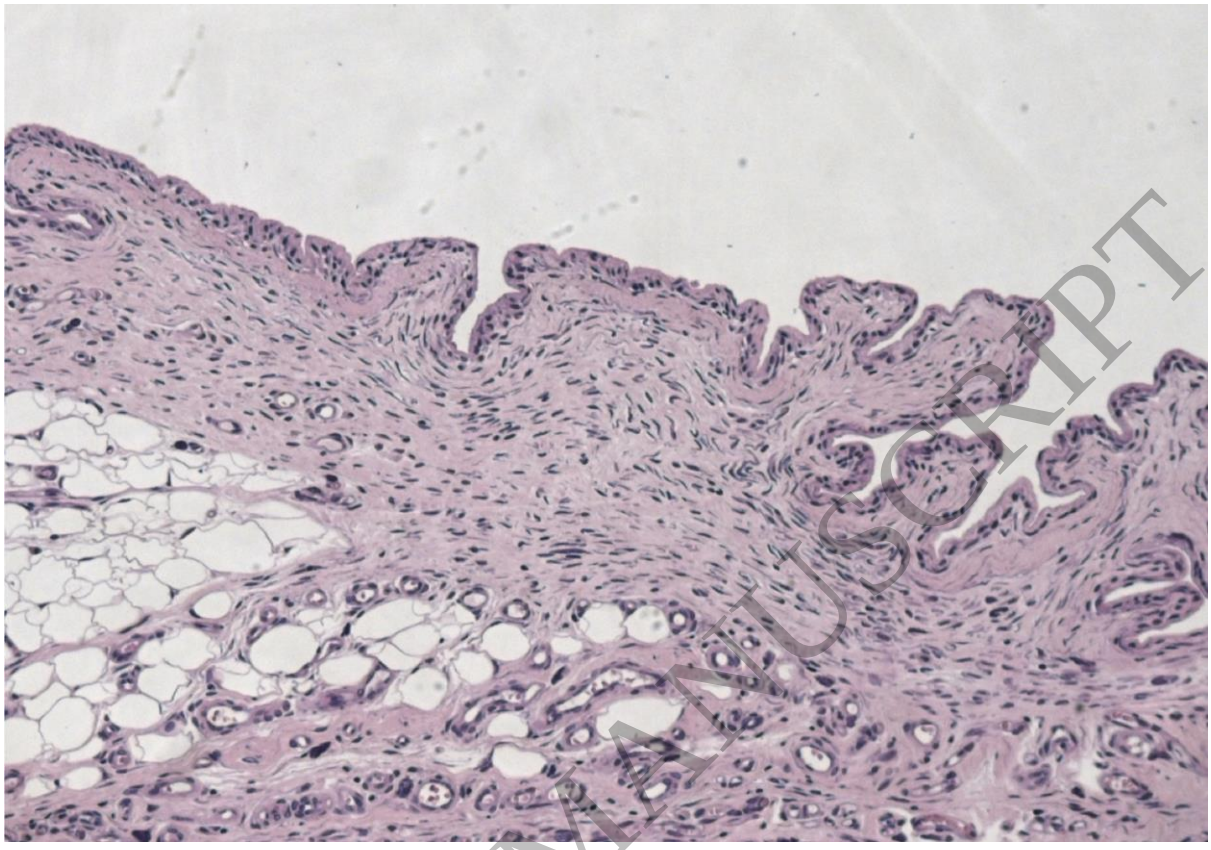

Figure 2D
159x111 mm (.33 x DPI)

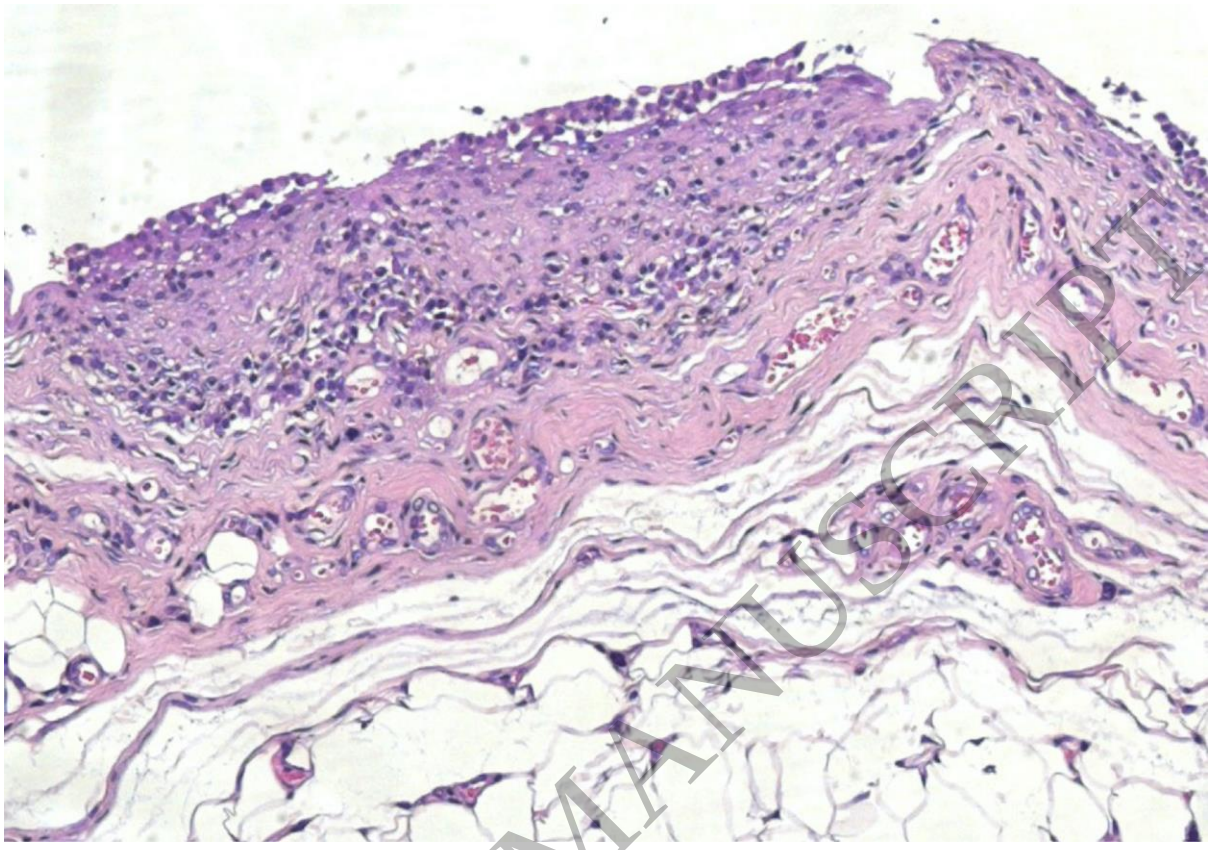

Figure 2E
159x111 mm (.33 x DPI)

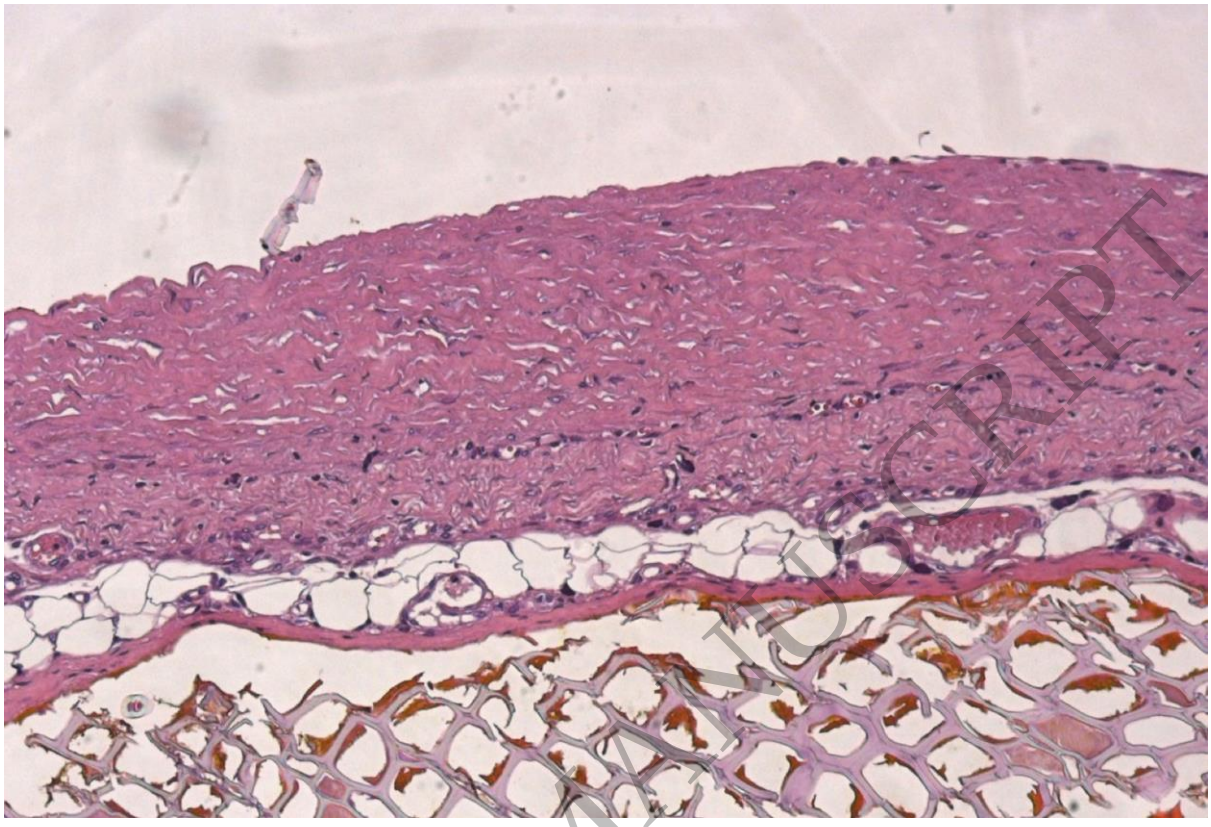

Figure 2F
159x107 mm (.33 x DPI)

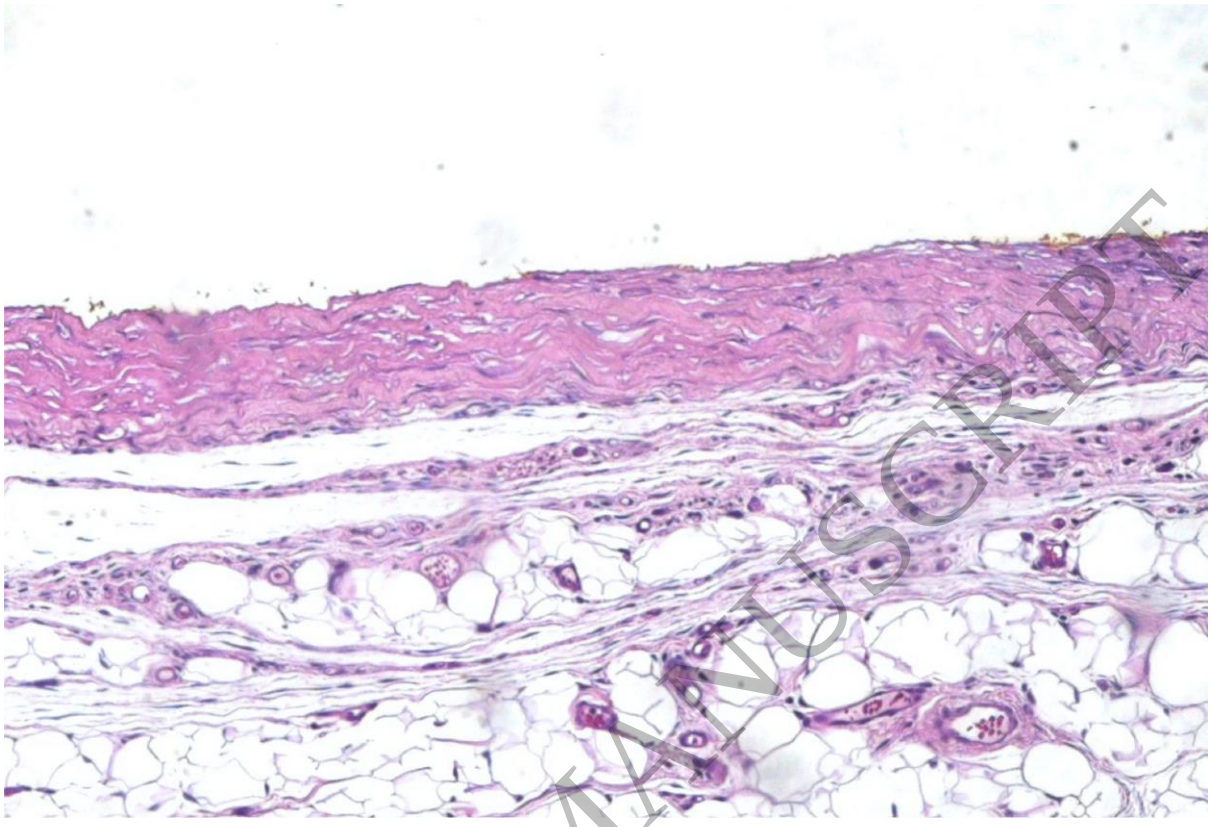

Figure 2G
159x107 mm (.33 x DPI)

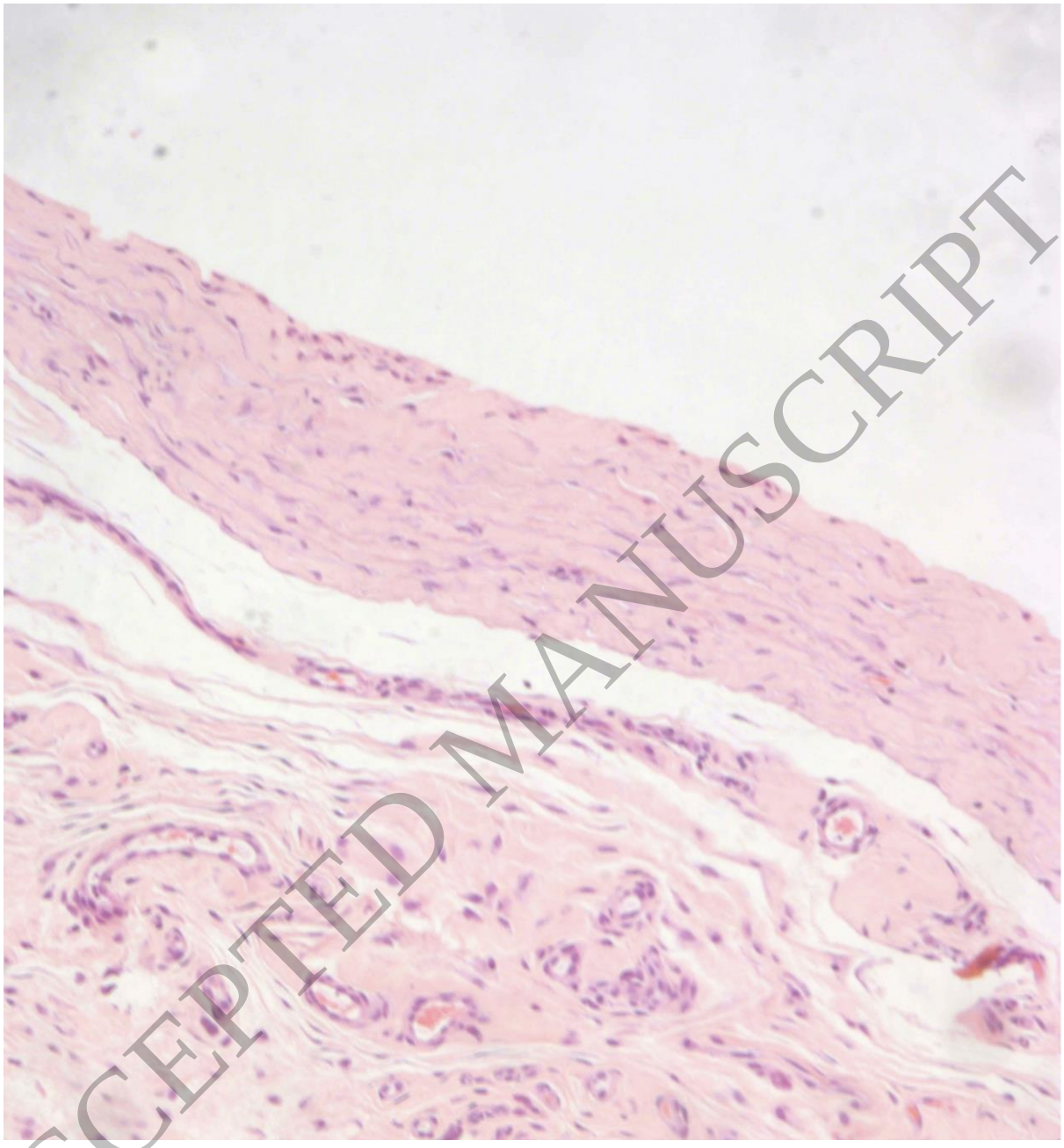

Figure 2H
159x171 mm (.33 x DPI)

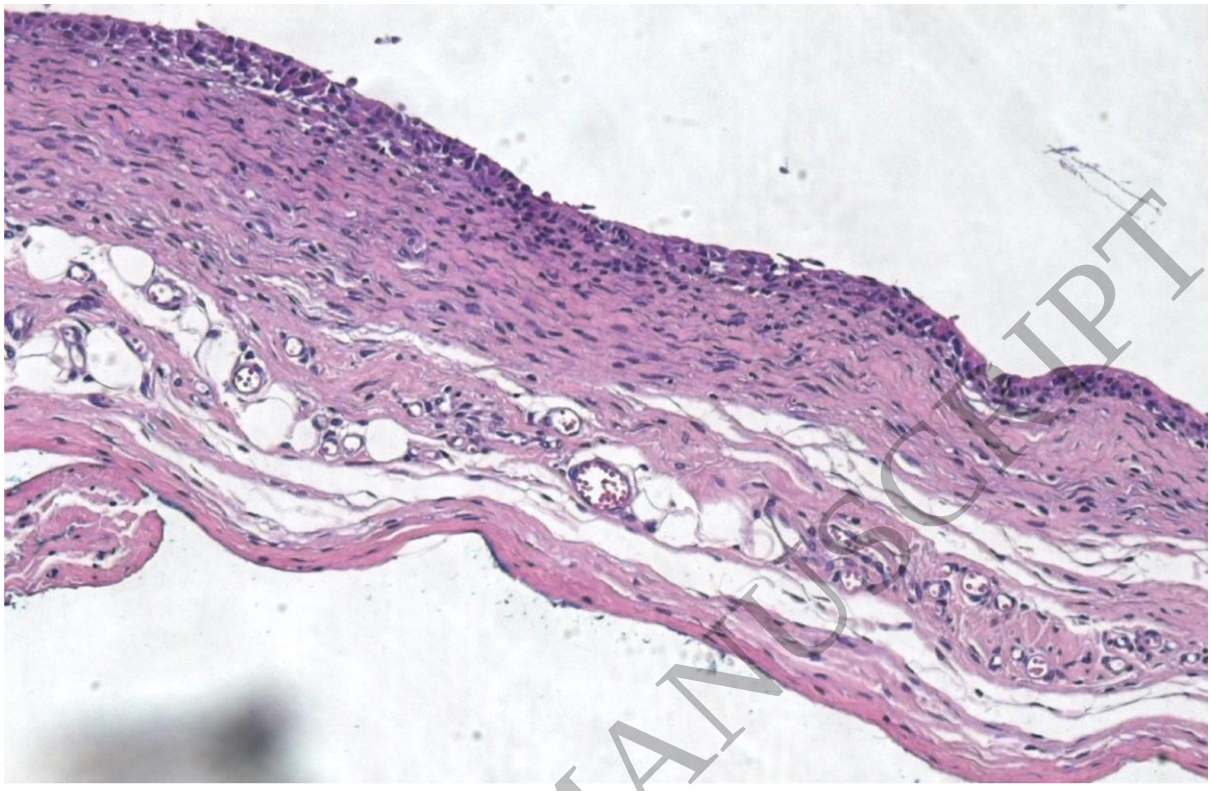

Figure 2I
159x103 mm (.33 x DPI)

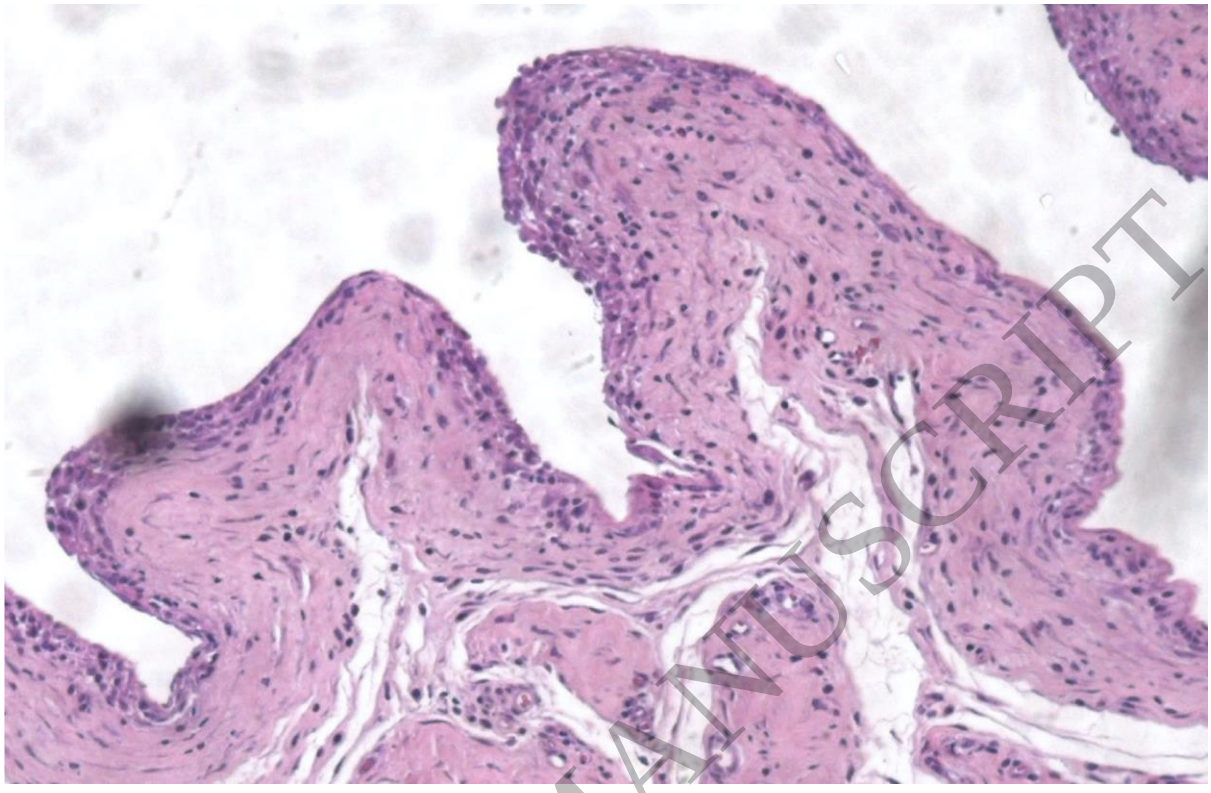

Figure 2J
159x103 mm (.33 x DPI)

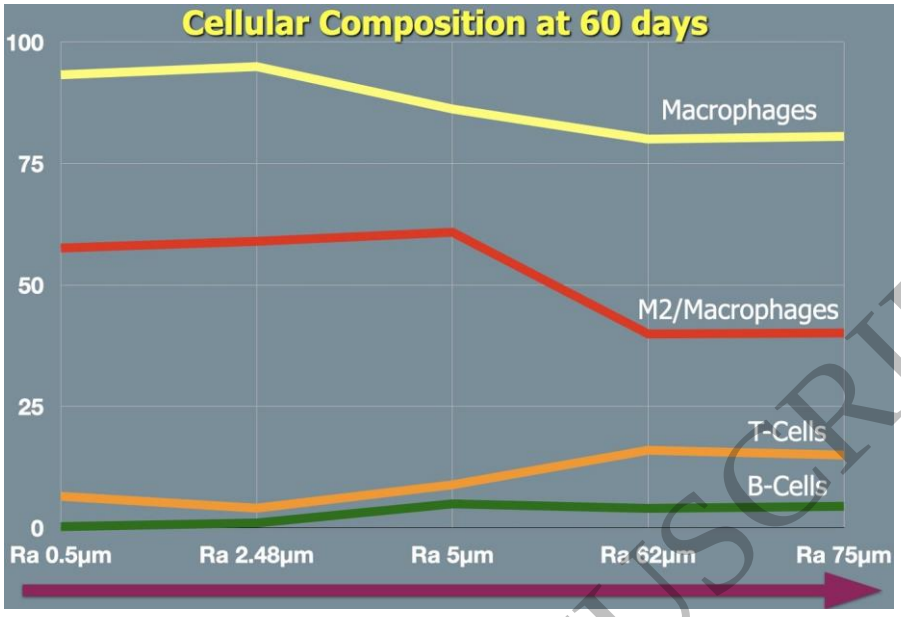

Figure 3
118x80 mm (.33 x DPI)

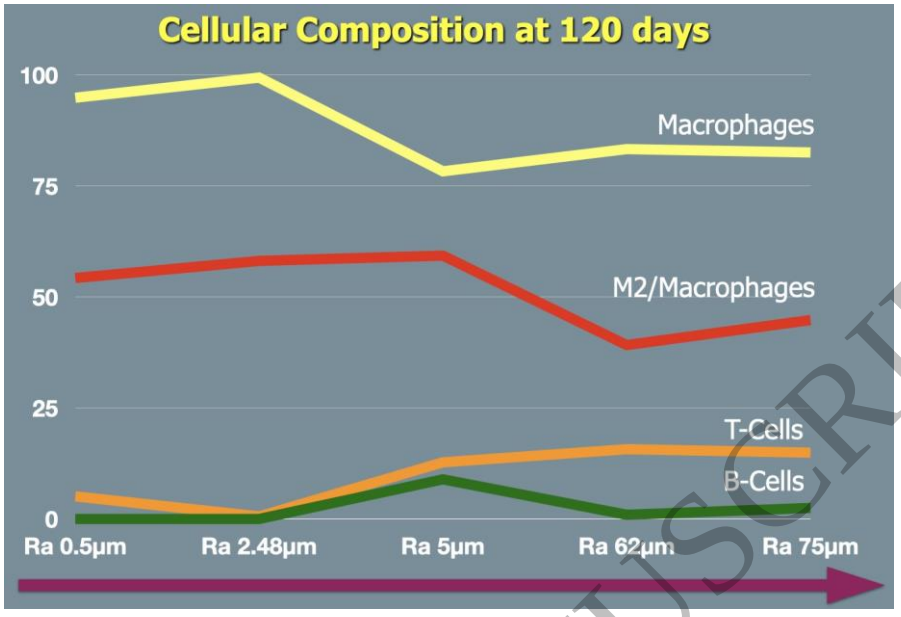

Figure 4
118x80 mm (.33 x DPI)