INNOVATIVE PERSPECTIVE IN SURGERY

Editor

Prof. Dr. Sibel AKYOL

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FOREWORD BY THE EDITOR

Today in order to recover patients' health, developing new and better treatment methods, applying new processes, and novelties and improvements in health products and services are of vital importance.

We prepared this book for the scientific world with the hope that it will bring an innovative point of view to develop solutions with novel ideas in surgery. I believe that it will be useful for scientists.

I owe many thanks to our dear authors who are experts in their fields as this book has been introduced as the result of a collective work reflecting the recent developments in surgery.

Prof. Dr. Sibel AKYOL

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CONTENT

CHAPTER I

THE IMPORTANCE OF 3D ANATOMY MODELING AND PRINTING TECHNOLOGY IN SURGERY

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1. Introduction

With the recent advances in technology, the data obtained from three-dimensional (3D) virtual reconstruction technology after CT (computed tomograph) or MRI (Magnetic resonance imaging) scanning is of great interest for planning surgical procedures.

Anatomy is essentially a discipline that deals with the three-dimensional structure of living things. Traditional or standard methods of teaching anatomy consist primarily of didactic lecture-based teaching, e-learning and small group teaching involving cadaver dissection, prosection and anatomical models. Clinically relevant approaches to surface and radiologic anatomy are also often incorporated into teaching.

The evaluation of the effectiveness of anatomy teaching is multifactorial, as determined by multiple studies. In some cases, animal specimens and three-dimensional laparoscopic dissection models are used instead of traditionally prepared cadavers. Regardless of the use of cadaveric models or alternative animal dissection models, a positive experimental outcome was observed when compared to regular didactic teaching sessions using plastic models.

The decline in the teaching of anatomy in undergraduate programs and the rise of technology now used in medical education has led to the research and development of new and innovative ways of teaching anatomy. Such approaches include computer-assisted teaching and computer-assisted learning as modern alternatives.

The entrepreneurial and innovative nature of human beings integrates entrepreneurship and innovation into life. Thanks to the combination of

innovation and entrepreneurship, three-dimensional software technologies have started to take an important place in our lives. Three-dimensional printing is a technological process in which a three-dimensional model, either personally created or readily available from anywhere, is solidly printed from a 3D printer.

Thanks to the integration of three-dimensional printers into life, models to be used as examples in the digital environment can be produced as concrete objects and used effectively.

Three-dimensional printers need existing three-dimensional modeling software to create physical objects from modeled objects and in this sense, computer-aided programs are used.

In medicine, various applications for three-dimensional printing technology have emerged, such as printing organs, printing body parts, bioprinting and computer-aided tissue engineering. In plastic surgery, these tools offer a variety of prospective applications for surgical planning, resident training and the development of custom prostheses.

Reconstructive surgeries can be extremely challenging for even the most experienced surgeons, especially due to the complex anatomy, the sensitivity of the systems involved and the uniqueness of each defect. The need to minimize the time for the surgical procedure, in addition to the need to reconstruct the defect in the best possible way, is crucial for surgeons to improve the patient's post-operative outcomes and well-being.

The patient-specific implant can be an effective solution in this case, designed to precisely fit anatomical defects or malformations. The need to perform personalized modeling and produce the required patient-specific implant has led and continues to lead to many innovations and technological advances in the medical field.

2. Undergraduate Anatomy Education

Evaluation of the effectiveness of teaching anatomy is multifactorial, as determined by multiple studies. Quantitative measures include short-term knowledge acquisition and long-term retention, in addition to student confidence and satisfaction.

The benefit of three-dimensional printing models in medical education is that data can be obtained from a wide variety of sources to produce an infinite variety of models. These models can be printed on a multitude of materials with the potential for additional customization after production. With sufficient

funding, a medical school could produce learning models suitable for use in a range of fields from anatomy and beyond.

One of the benefits of three-dimensional printed is the re-emergence of anatomical variation in the emergence of reduced cadaver dissections. A haptic experience could be included where three-dimensional printing models could be created from existing three-dimensional images, providing students and lecturers with the ability to handle and manipulate these variations.

Many hospitals around the world are experiencing difficulties with surgeries. One of the strategies proposed to reverse this situation is to increase the rate of medical students practicing during the education process and to ensure that they are exposed to the field earlier. In this case, three-dimensional modeling and three-dimensional printed designs offer a more realistic and innovative approach.

In a study by Fasel et al. dissection of two cadavers was performed and Computed Tomography (CT) was taken after the necessary analog measurements were made. Then, two students took measurements of the selected anatomical structures with Mimics and Osirix three-dimensional software and made three-dimensional reconstructions. Three-dimensional prints were obtained from these three-dimensional models. Necessary measurements were made on these three-dimensional replicas. They were subjected to standard statistical analysis (Wilcoxon two-tail paired test) to reveal the differences between the values obtained by the three-dimensional modality.

As a result of this study, a qualitative comparison of the students' manual CT segmentation and digital three-dimensional reconstructions based on anatomical reality showed an excellent correlation. They reported that the measured morphometric values differed by less than 2 mm from the values measured on CT images and three-dimensional printed models measured on cadavers. The satisfaction score of the students at the end of this study was 5.8 on a scale of 1-6.

The advent of three-dimensional printing of human material, cadaver dissection, plastination, computer simulation and the use of anatomical models as an educational tool holds great promise. The findings suggest that three dimensional printed models can be equally effective for teaching anatomy as cadaveric prosections.

Many studies have shown that three-dimensional printed models can be effective teaching tools. Therefore, it is recommended to use three-dimensional

models whenever possible to provide anatomy instruction where previously only anatomical atlases or other two-dimensional images were used.

Medical education is subject not only to economic constraints but also to ethical, legal and cultural concerns that limit the availability of cadavers. Three-dimensional prints derived from modern technology and three-dimensional models offer possible solutions in this area and are used to model human anatomy in a variety of settings.

3. Three-dimensional Models and Printing Technology in Diagnosis and Treatment

Medical imaging techniques used for diagnostic practice significantly assist radiologists in the detection and interpretation of abnormalities in patient anatomy. Therefore, the application of computer-aided diagnosis must be successful in order to understand the medical image.

Across various surgical disciplines, rapid prototyping has shown significant advances in the diagnosis and treatment of various diseases due to a better understanding of the pathologic structure and a better understanding of the complex underlying conditions. Such modeling allows for more rigorous preoperative planning, while learning more about the specific anatomical components before performing a procedure on a patient can improve efficiency.

Three-dimensional modeling and three-dimensional printing is a rapidly advancing technology that represents an important technological achievement that can be useful in various biomedical applications. In the field of surgery, three-dimensional models and prints derived from them are envisioned as an important step forward in surgical planning, education and training. 3D printed models are considered high-quality and efficient training tools.

There are studies on this subject in many surgical branches and the importance of these models is emphasized. For example, as a result of various studies, researchers have reported that the use of modeling and three-dimensional printing in plastic surgery is applicable to improve the accuracy of preoperative surgical planning, as well as to improve and facilitate the quality of diagnosis, especially in cases of extremity, craniofacial and maxillofacial surgery.

Three-dimensional printing technologies, which have many different types of applications in the medical field, can be used in many areas such as anatomical model production, special surgical device design and personalized implant or prosthesis production.

These three-dimensional "biomodels" containing anatomical structure features are used in diagnosis, surgical operation planning, simulation, neurosurgery and medical education.

Before making the most appropriate decision during surgical planning; calculating the possible risks, simplifying a structure with complex anatomy and making it understandable are necessary for the success of the operation.

In addition, thanks to these models obtained in all surgical branches, the error rate to be made is reduced. Thus, it makes surgical branches more attractive.

Surgeons have reported in several studies that the models are potentially useful in preoperative planning of surgery and aid intraoperative navigation. In addition, the models have been evaluated by patients to help them understand their disease and have also been reported to be useful in these studies. Patients reported in the results of these studies that the models were helpful in understanding anatomy, pathology and surgical risk.

4. 3D-Printing İn Pre-Operative Surgical Training

In addition to the potential of three dimensional printing for the delivery of undergraduate teaching with respect to both normal and abnormal anatomy, many investigators have acknowledged a possible role for three dimensional printing in the training of postgraduates in clinical procedures.

In the field of surgery, the potential for three dimensional printed models has been explored for advanced simulation training that could be patient-specific, incorporate pathology and can share compatibility with surgical implants.

Three-dimensional printing, which enables detailed visualization of complex underlying conditions in the human body, can be very easily applied to the field of surgery. Among various surgical disciplines, rapid prototyping has shown significant improvements in the diagnosis and treatment of various diseases due to a better understanding of the pathological structure and a better understanding of the complex underlying conditions. With these advances, it allows for more meticulous preoperative planning. Learning more about patient-specific anatomical components before performing a procedure can improve efficiency.

The patient-specific planned and acquired models can help surgeons simulate the operation on the model, including measuring the anatomical numerical value and selecting the shortest path to the area to be operated on. The whole model not only gives the surgeon a true visual experience, but also a tactile experience that a two-dimensional image cannot provide.

Another benefit of printed models derived from three-dimensional models in surgical planning is that they can be used to rehearse complex and delicate procedures. Three-dimensional printed models give surgeons the opportunity to familiarize themselves with the approach and anticipate all problems in detail before surgery.

The use of three dimensional printed models as preoperative training tools enables multi-planar visualization of anatomy and associated pathology. When integrated with patient-specific models, three dimensional printed creates clear advantages over traditional cadaver models as it allows surgeons to go through a realistic simulation of the individualized procedure required before the actual surgery.

This type of training has many benefits, including reduced operative time and the ability to predict intraoperative complications. They also aid in preoperative planning. Therefore, when three dimensional models are used in combination with other resources such as video recording and feedback, this approach provides optimal training in many areas, both surgical and medical.

Simulations offer the ability to create realistic medical scenarios for surgical training procedures, resulting in errors that pose no risk to patients, especially in challenging surgical operations.

Historically, animal models have been used in the medical field both for education and training in the surgical branch and often in scientific research. However, animal experiments have some limitations such as ethical concerns and costs. For this reason, it is not suitable for large-scale studies under today's conditions.

Simulation training with three-dimensional models, which are different from traditional anatomical models derived from both human and animal cadavers, will help to predict intraoperative complications, select the best surgical approaches, and improve the skills of young surgeons without the risk of adverse events. Moreover, after adequate training with three-dimensional models, surgeons will perform real surgeries with more confidence.

Thanks to these models, having a modified model to simulate the patient's anatomical structures in the preoperative environment as well as the anatomical structure that will occur after surgery can be valuable in terms of making sure that the patient will meet expectations. This patient education should be shown to the patient, especially before the plastic surgery operation. The purpose of using these models is to enable the patient to better understand the intended procedures and outcomes. This can be thought to increase both doctor and patient satisfaction after the operation.

Rapid prototyping across various surgical disciplines has shown significant improvements in the diagnosis and treatment of various diseases due to a better understanding of the pathological structure and a better understanding of the complex underlying conditions. These resulting models allow for more rigorous preoperative planning.

Learning more about patient-specific anatomical components before performing a pre-operative procedure can improve efficiency. This not only simulates the operation, but also allows for preoperative planning. As a result, it prevents a possible fatal error at the time of surgery and shortens the operation time.

Surgeons are expected to have a thorough understanding of human anatomy, especially the topographical relationships of different structures and tissues to each other. Anatomical expertise is a prerequisite for performing a procedure; this technology enhances the learning experience of surgical residents in training and can improve patient education. The use of a two-dimensional or three-dimensional image on a flat screen provides a more intuitive perception of various complex anatomical details, which can sometimes be insufficient.

Three-dimensional printing can help surgical residents better understand different anatomical structures and pathologic conditions. Furthermore, these three-dimensional models allow for intensive training before an operation. Thanks to these three-dimensional models and prints, surgical residents will be able to train in patient-specific operations in general, as well as develop a surgical plan necessary to perform many specialized procedures such as complex microsurgery and pediatric plastic surgery.

The theoretical cost of using this technology in resident training will include the cost of purchasing a 3D printer in addition to material costs. It is predicted that the use of these materials will increase with the developing technology and accordingly, the cost will decrease due to its accessibility.

5. Creating a Three-Dimensional Model from a Medical Image and Obtaining Three-Dimensional Prints

Three-dimensional printing technology has developed rapidly over the past few decades. Meanwhile, the application of this technology has expanded beyond engineering to almost all disciplines, including medicine. Numerous studies have been conducted on the medical applications of 3D printing in many surgical branches such as neurosurgery, orthopedics, maxillofacial surgery,

plastic surgery, cardiovascular surgery, ophthalmology, tissue engineering and many other fields.

There are many methods for obtaining image data by scanning parts of the human or animal body. The main visualization techniques used for this are CT and MRI. CT is one of the quality control methods used in industrial applications for internal and external measurements of parts with complex geometry.

Three dimensional printers need existing three dimensional modeling software to create physical objects from modeled objects and in this sense, computer-aided programs are used. Visualization techniques must be used correctly to create a successful three-dimensional anatomical model. Due to the possibility of mismatch between the image from the anatomy and the generated model due to low resolution, the region where the visual data is selected is very important. For this reason, the processing of image data plays a critical role in enabling experts to reach the correct diagnosis. In order to create three-dimensional images from CT and MRI data, objects need to be modeled with their internal features and surface interactions.

CT sections taken from any anatomy are passed through some stages according to the volume rendering method and a visualized model is created. These sections obtained independently from each other can be separated and extracted by image segmentation techniques.

Digital images from CT in DICOM (Digital Imaging and Communications in Medicine) format are transferred to the computer programs used. If bioprinting is desired from the obtained three-dimensional models, they are transferred to a three-dimensional printer.

Three-dimensional printing, which was first applied as a non-medical science in the field of engineering in 1986, has grown tremendously in its current integration into the field of health care, especially with the recently developing technology. Three-dimensional printing has been shown in many studies to reduce healthcare costs and promote higher quality patient care. The application of three-dimensional printing in combination with post-processing computed tomography and magnetic resonance imaging has opened several avenues for medical and related healthcare fields, including prosthetics, surgery, radiation therapy, medical dosimetry, biomedical research and organ transplantation.

Additive manufacturing has numerous application areas, one of the most important being biomedical engineering. three dimensional printing is often preferred over traditional manufacturing methodologies when developing subject-specific implants and medical devices. In this application, it aims

to provide a process flow detailing all stages starting from the acquisition of radiological images from different imaging methods, such as computed tomography and magnetic resonance imaging, to the validation process of the output of bone morphology and finite element analysis.

In design processes, the finite element method is widely used to determine the mechanical properties and structure of the prototype of interest. The bio-accuracy of the models is tested by comparing the Finite Element results with experimental results. The result of the obtained three-dimensional simulations can be cross-validated with other FE models that have already been validated based on experimental results.

The 3D printers can be classified into various types according to printing speed, strength, printing material, and the working principle. In general, 3D printers have mainly three different types: Selective Laser Sintering (SLS), Fused Deposition Modeling (FDM) and Stereo-lithography (SLA).

The SLS printers use powdered material to print new objects and fuse them via laser waves. The principle of the FDM printer is that the heated plastic is extruded from the printer head. The nozzle moves to the predetermined points and leaves the molten material to these locations layer by layer. The SLA technique performs the printing process by hardening certain areas of the photopolymer resin layer through the ultraviolet laser beam. Each method has various advantages or disadvantages compared to each other.

Three dimensional printers have been used for many medical purposes and for the production of anatomical structures using CT scans in many tissues such as bone tissue, blood tissue, cartilage tissue. Some of these purposes have recently started to be used in three dimensional printer technology in many studies such as subject-specific implant designs, preoperative planning, various visual models and experimental studies to be used in medical education.

Deciding on the type of three dimensional printer and the material to be used according to the type and purpose of the application is a very important step. In addition, in preoperative planning applications, SLA or SLS techniques are more applicable methods due to their low processing time, low part cost, optimum level of detail and more practicality.

Multiple programs are used for all these processes, from image processing to three dimensional printing, and the transitions between these programs should be considered when deciding which tools to use. It is very important to use the correct file format when transferring processed files between these programs. This is because orientation, mesh distributions and surface geometries may

vary in different formats to avoid further confusion. With these file formats, the models should be transferred to the analysis software accordingly.

In many studies on this subject, findings such as shortening the operation time and less blood loss have been obtained by making a logical preoperative planning with personalized models and prints. It has also been reported that preoperative three dimensional printed models increase surgical success in implant applications.

The images obtained from CT scans were reconstructed using segmentation tools and implants were applied on these models for preoperative planning purposes, and many studies have shown that they increase the surgeon's surgical success.

Many studies show that today, with the developing technology, the quality of the three-dimensional models obtained by personalized three-dimensional models to be exactly the same size as the anatomical structure and accordingly the quality of the three-dimensional prints obtained is increasing.

In conclusion, with advances in affordable three-dimensional printing technology, three-dimensional reconstruction and patient-specific three-dimensional printed models have established a crucial role in the medical field for both educational purposes and procedural planning. Three-dimensional printed models will provide physicians with greater three-dimensional perception and haptic feedback, as well as a team-based approach to operational planning.

However, performing an effective three-dimensional reconstruction requires an in-depth understanding of the software features to accurately segment and reconstruct the relevant human anatomy from previously acquired image data from multiple modalities such as computer tomography, three-dimensional angiography.

A better understanding of this technology is by developing techniques and tricks specific to surgical units, interventional radiology. And this can benefit radiologists by establishing a benchmark for determining when and how to use the details obtained.

6. Development of Custom Prosthetics

Customized prosthesis development is used in many branches such as cardiovascular surgery, plastic surgery, neurosurgery and orthopedics. Perhaps the most exciting aspect of this technology is the process of constructing and building the implants or prostheses that will be used.

The use of implants and prostheses with three-dimensional prints is most commonly applied to patients who have lost their limbs after orthopedic surgery. In many studies, simulation of fractures or pathological conditions in orthopedic surgery is used very frequently.

Based on the imaging data or a three-dimensional printed model created from these images, a reasonable body position and surgical approach are selected.

Especially in fracture operations, the detailed presentation of the anatomy of the region, the structural feature of the fracture, the change in the anatomy of the region caused by the fracture, the planning of the surgery and the pins, implant or prosthesis to be used before the moment of surgery.

After orthopedic surgeries, three-dimensional printing materials are frequently used in the production of prostheses or custom-made pins created depending on the anatomy of the extremities or the region where the defect occurs. Because this technology is highly preferred both in terms of cost and the short duration of the production phase.

People with disabilities necessarily require a variety of assistive devices, especially for use on the extremities, such as hand or foot orthoses, ankle orthoses and prosthetic sockets. 3D printing technology provides the freedom to customize these assistive devices. The most important recent development in 3D printing technology is the production of a composite lower limb prosthesis and test socket.

These prostheses and test socket have sufficient mechanical strength with durability properties to support implantation and achieve its goal. For this reason, personalized implants obtained from these three-dimensional models are of great importance for disabled individuals. Obtaining these implants through three-dimensional printing provides great convenience to disabled individuals due to its low cost and short production time.

In plastic surgery, the use of customized prostheses for the reconstruction of various facial structures has been successfully applied many times and continues to be applied. While three-dimensional printing can be used in bone reconstruction, it can also be useful for the replacement of soft tissues.

This technique has been used in auricle reconstruction in patients with anotia, where a mirrored scan of the contralateral ear is used to create an auricle model. This technique also has the potential to produce tissue scaffolds for cellular growth and the creation of vascular networks that may alter the incidence of flap failure.

In hand and foot surgery, this technology can be used to create prosthetic parts of the upper and lower extremities specifically tailored to the functional needs and anatomy of patients.

In another study, three-dimensional printing technique is frequently used in cardiovascular surgery. In the field of cardiovascular surgery, it is useful in many areas such as heart valve reconstruction or micro-vessel production.

In their study, Kang et al. created a three-dimensional aneurysm model by taking CT angiography from 24 patients diagnosed with intracranial aneurysms and converted it into three-dimensional printing. In the models, they successfully replicated the circle of Willis artery, the posterior circulation arteries and the structure of the skull base, including the anterior clinoid process, posterior clinoid process and sphenoid. The location and shape of the aneurysm from both CT images and hard copies were compared and reported to be consistent with each other.

Cranioplasty is frequently performed for defects in brain surgery patients. Those who undergo craniectomy for various indications ultimately require reconstruction of a cranial defect. In 20-50% of cases, the patient's autologous bone cannot be replaced due to infection, fragmentation, bone resorption or other reasons. In these cases, a synthetic bone flap is made to repair the defect.

Unfortunately, large defects or bony areas with complex contours are difficult to reconstruct with the "free hand" technique during surgery. This requires the use of advanced manufacturing methods to create patient-specific implants. While patient-specific implants are available from some medical device companies, cost and production time are significant limitations that prevent their wider adoption.

Production time often takes weeks, limiting the use of commercial solutions in cases of trauma or when emergency reconstruction is required. However, implants obtained from three-dimensional printing are preferred because they are both more affordable and can be produced in a shorter time. Considering all these, the use of this technology is increasing day by day in neurosurgery, as in other surgical branches, due to the fact that implants obtained by three dimensional printing are both cheaper and faster accessible.

In oral, dental and maxillofacial surgery, this technology is frequently used in computer-aided prefabricated implant design and production system to improve trauma or aesthetic outcome.

Whether the modeled materials to be created are suitable for the patient's mouth shape, mandible structure or face is also observed during modeling.

As can be seen, three-dimensional models and three-dimensional printing models obtained from them are used in many surgical branches to provide implant and prosthetic support in defects or organ deficiencies.

Three-dimensional printing technology has been explored in recent years with numerous potential application methods. The concept of three-dimensional printing first started to emerge in the late 19th century, followed by further development in the 1980s. The term three-dimensional printing is the common name for rapid prototyping (RP), which is regularly used in the engineering field. It maps two-dimensional printing to stereoscopic printing, which is a product of the combination of traditional two-dimensional printing technology and additive manufacturing process.

The use of three-dimensional printing technology in applications such as organ printing, body part printing, bioprinting, computer-aided tissue engineering in medicine has emerged with the developing technology. Organs and functional body parts are created by three-dimensional printers working with various principles such as inkjet techniques.

Compared to traditional manufacturing, three-dimensional printing technology offers several key advantages, such as being faster and requiring no molds or production lines. This technology is widely applied in the field of engineering, from large-scale industrial manufacturing to the production of small plastic parts for the electronic communications industry.

The use of RP technology has many potential applications in mechanical engineering, aerospace and automation, among others. Inspiringly, a number of applications of this technology have been proposed for use in the medical field and have found application in many clinical areas in recent years.

It is seen that three-dimensional anatomical models provide significant benefits for surgeons to determine the most appropriate method to successfully complete vital surgeries. Thanks to additive manufacturing technology, the internal structure of three-dimensional anatomy that can be printed transparently can be understood more easily. The process that results in the transformation of medical images into physical objects involves radical developments for the future of modern surgery, despite negative factors such as high production costs and long printing time.

In the coming years, with the developments in material technology, three-dimensional biomodels with mechanical and physical behavior similar to the living anatomical structure will become possible. As with any new manufacturing technology, there are some limiting factors in additive manufacturing. These

include the high cost of producing the three-dimensional model, the need to protect patient-specific anatomical information in the transfer of information to the manufacturer, the long model production time and the need for additional processes to give the final shape to the part.

In addition, the existence of some gaps that are captured on CT and are not recognized in the visual data or appear closed is one of the biggest challenges encountered in surgical applications.

Thanks to additive manufacturing technology, the internal structure of three-dimensional anatomy that can be printed transparently can be understood more easily. Surgeons can rotate the resulting three-dimensional model in their hands to observe abnormalities in the body from different viewpoints, which can greatly reduce the visual errors produced by traditional two-dimensional images. The process that results in the transformation of medical images into physical objects involves radical developments for the future of modern surgery, despite negative factors such as high production costs and long printing time.

These three-dimensional models and three-dimensional materials printed from three-dimensional printers enable surgeons to conduct research, train surgeons on education, and improve preoperative planning without posing a risk to patients.

Three-dimensional printers are a new and emerging technology capable of producing physical objects from digital files. Reduced hardware costs have made this technology suitable for use in the office environment.

There are numerous applications in medicine, including the printing of skin, bone and whole organs. Potential uses in all surgical specialties range from surgical planning and training to prosthetic device design and development.

Both medical students and surgical residents should learn how to manage volumes of radiological data and print them in three dimensions using image processing tools commonly used in clinical practice. And thus they will be actively involved in the creation of state-of-the-art anatomical models used in contemporary surgical practice. Thus, they will have the opportunity to improve themselves both in their medical education and in the field of surgery and to perform safer surgeries.

Three-dimensional modeling and printing from these models is a well-established rapid prototyping, additive manufacturing technology. This technology appears to offer a revolutionary opportunity to create parts and components in bulk from different materials that exhibit desired mechanical and physical properties. As a result, three-dimensional printing is recognized

as an important technological innovation in medicine with a wide range of applications to overcome current limitations, while at the same time providing significant improvements in state-of-the-art technologies.

Obviously, it can be used to create three-dimensional anatomical models for better preoperative planning, optimization strategies for device testing and surgical training recommendations. Furthermore, the creation of a prototype three-dimensional model based on patient-specific analytical image findings offers micro-scale anatomical precision and time-saving reproduction. So far, the most important application of three dimensional printing in the medical field has been the design and development of medical devices and instruments.

Recently, three-dimensional printing has attracted great interest from surgeons, who can plan complex operations better and more efficiently through the use of three-dimensionally printed anatomical models. These models can be used for training purposes and are clearly easier to use as well as more cost-effective than cadaveric models.

All surgical specialties face difficulties when operating on complex anatomical structures with conventional treatment, and revision surgeries may occur in complex cases with multiple fractures, especially in orthopedic surgery. The surgeon requires an understanding of the complex geometry of the foot.

Three-dimensional printing technology is rapidly increasing its use in the biomedical field due to its many advantages such as freedom of design, complex structure production, cost effectiveness and ease of use. Three-dimensional modeling is used for a variety of applications in the biomedical field, such as the fabrication of hydrogels, scaffolds, vascularized soft tissues and bone implants. The role of 3D printing in biomedicine is becoming increasingly vital in drug formulation, surgical planning, implants, prosthetics-orthotics, tissue engineering, anatomical model and organ printing.

Advances in science and technology have been invaluable in improving medical diagnostics and treatments. In recent years, the development of three-dimensional printers capable of fabricating any object has led to their application in various industries, including medicine. The process of three-dimensional printing begins with the acquisition of image information about the object to be produced. This image information can be obtained by directly drawing the desired shape.

In medicine, Computed Tomography or Magnetic Resonance images are often used for this purpose. It is predicted that the integration of medical images, which are widely used in patient diagnostics, with the printing technology

obtained from the latest three-dimensional models is very helpful for diagnostic and treatment purposes and will provide more benefits with the developing technology.

Another application of three-dimensional models is their use as a tool to explain procedures to patients during medical consultations, a practice that has been proven by many studies to increase patient satisfaction and instill a sense of involvement in medical staff.

As can be seen, many studies have shown that three-dimensional models and three-dimensional printed models derived from them are very close to the actual anatomical structure. The program provides early and interactive exposure of medical students to a surgically relevant trend. With the developing technology, the use of this technique is becoming more and more widespread and its use in the field of surgery is expected to increase day by day.

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CHAPTER II

ALTERED IMMUNE MECHANISMS AFTER THE IMPLANTATION OF BIOMATERIALS PRODUCED BY 3D TECHNOLOGY

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1. Inflammatory Response After Surgical Trauma and Implantation

The immune system is a complicated mechanism that protects the organism against antigenic structures, infections, and homeostatic imbalances. The immune system consists of the innate and specific immune system, which plays an important role in the response to the foreign which is considered "dangerous".

The inflammatory response begins with the migration of immune cells to the traumatic site (infection, pathogens, etc.) and the triggering of phagocytic and complementary activation. These responses may occur not only against antigenic structures but also after surgical traumas. Infection and tissue damage that occurs after surgical intervention, constitute a dynamic process that triggers immune responses, as in physiological mechanisms. However, the mechanism of similar immune responses against pathogens and surgical trauma is not clearly understood.

After surgical trauma, tissue healing and restoration of organ integrity are provided by the stimulation of the specific immune system following the secretion of proinflammatory cytokines, phagocytic activation, apoptotic events, and complement activation.

The fact that the inflammatory responses to traumatic events in the organism are limited and timed at a certain level, that is, a certain balance is established, ensures that the antigenic stimulus is eliminated without damaging the organs. While limited immune responses accelerate the healing process, excess immune reactions cause tissue damage.

As stated, the first immune response begins with the migration of nonspecific immune cells as a result of the organism becoming predisposed to septic complications due to surgical trauma. Following the release of proinflammatory cytokines synthesized by these cells, activation of specific immune cells and the formation of a compensatory anti-inflammatory or immunosuppressive response (CARS: Compensatory anti-inflammatory response syndrome) occurs. These can trigger systemic inflammation. Systemic inflammation, as seen here, is an excellent example of how the innate and specific immune systems work together.

The specific immune response intensifies the innate immune response and makes it focused. This can lead to multiple organ dysfunction syndrome (MODS) in some susceptible organisms. Sepsis, systemic inflammatory response, and MODS cause postoperative mortality in the intensive care setting.

Changes in hemodynamic, metabolic, and immune responses occur in the postoperative period. The immune defense critically depends on cytokine balance and macrophage-T-cell interaction. The immune dysfunction caused by surgical trauma is due to the deterioration of these homeostatic mechanisms. (*Figure 1*)

1.1. Cytokines and Chemokines

Depending on the extent of surgical trauma, endothelial and epithelial cells, as well as neutrophils, macrophages, and lymphocytes produce potent proinflammatory cytokines, particularly tumor necrosis factor-α (TNF-α), interleukin (IL)-1β and IL-6. Chemokines, which lead to leukocytes and stem cells chemotaxis in traumatic events, play an important role in the biological processes by triggering leukocyte migration, angiogenesis, and leukocyte degranulation.

There is a dramatic increase in the secretion of chemokines during inflammation. The most significant stimulus for chemokine production is early proinflammatory cytokines. The major stimulants that increase the synthesis of chemokines are IL-1, LPS (lipopolysaccharide), TNF-α, interferon (IFN)-γ, and IL-4. Chemokines play an active role in leukocyte-endothelial cell interactions,

T and B cell maturation, T-B cell communication, and the formation of the primary immune response, immune control, immune tolerance, and immunity after surgical trauma.

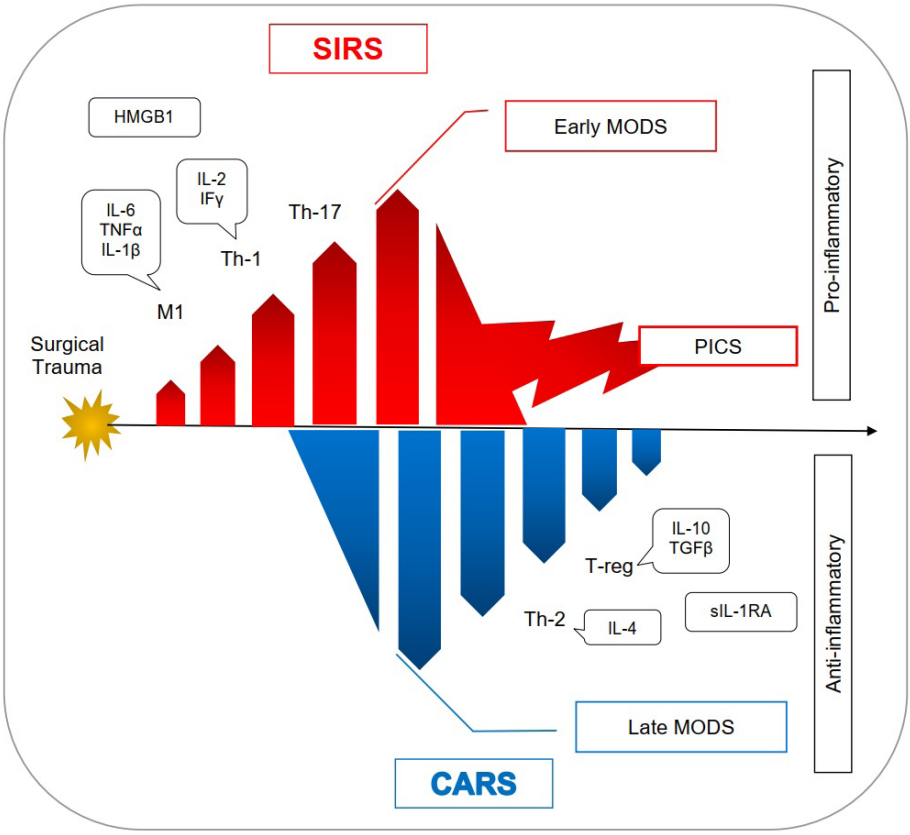

Figure 1. CARS: Compensatory anti-inflammatory response syndrome, HMGB1: High mobility group box protein 1, IFN: Interferon, IL: Interleukin, M: Macrophage, MODS: multiple organ dysfunction syndrome, SIRS: Systemic inflammatory response syndrome, T: T lymphocyte, TGF: Transforming growth factor.

In the inflammatory process that occurs after implantation, chemokines lead leukocytes to migrate from the blood to the tissue, their accumulation, and activation at the site of the inflammation. The recruitment of neutrophils, monocytes, and macrophages to the mucous membranes and their involvement in inflammatory processes are also substantially dependent on chemokines.

Two main chemokine/related receptors of the subgroups of monocytes from the blood, bone marrow, and spleen are associated with surgical trauma. These are CCL2/ CCR2 and CX3CL1/CX3CR1. CCR2 and CX3CR1 are the

two chemokine subgroups that play an active role in the healing process of the tissue, especially after implantation.

Interestingly, it has been shown that macrophages are the main source of VEGF-A in early tissue repair.

CXC chemokines, growth factors, adhesion molecules, and cytokines released from cells and tissues play a significant role in inflammation, angiogenesis, tissue repair, and new tissue formation.

After implantation, substances such as PDGF (Platelet-derived growth factor), and VEGF-A (Vascular endothelial growth factor A) released from thrombocytes, and chemokines from the CXC family like CXCL1, CXCL5, CXCL7, and CXCL4 initiate the inflammatory process in the extravascular tissue and form a barrier against microorganisms.

CXCL1 expressed on the vascular wall facilitates neutrophil diapedesis. Co-expression of CXCL1 and CXCL8 promotes neutrophil migration to the implantation site. Neutrophils coming to the region expedite phagocytosis by synthesizing reactive oxygen derivatives and proteinases. In this way, cell debris, degraded products, and microbial residues are cleared from the area of inflammation.

In the process of angiogenesis and neovascularization after phagocytosis, CXCR2 receptor expression occurs in endothelial cells and CXCL8 expression gradually increases between the 1st and 4th days. In this way, granulation and numerous capillaries are formed in the implant area.

Following the accumulation of neutrophils, monocytes and macrophages come to the region as a result of the CCL2 and CCR2A receptor interaction. The production of CXCL12, which is synthesized from fibroblasts and keratinocytes under the inhibitory effect of IL-1 and TNF-α, decreases gradually until the 6th day. Then, starting from the 14th day, a large number of lymphocytes accumulate in the region under the effects of CXCL9 and CXCL10.

Alteration of nonspecific immune responses causes coagulation defects, increased inflammation, edema formation, and barrier degradation. These changes can increase hypoxic conditions, accumulation of metabolites, and bacterial invasion.

1.2. DAMPs and PAMPs

After tissue damage, a local inflammation occurs in response to damage-associated molecular patterns (DAMPs or alarmins) and pathogen-associated molecular patterns (PAMPs). DAMPs are produced endogenously, and

PAMPs are produced exogenously. Both contain formyl peptides as well as bacterial (PAMP) or mitochondrial (DAMP) DNA. DAMPs directly bind to the glycocalyx. DAMPs are recognized by pattern recognition receptors (PRRs), such as mannose-binding lectin (MBL), TLRs, and scavenger receptors.

Endogenous danger signals are usually secreted from necrotic or stressed cells, which are the damaged extracellular matrix (ECM). Known DAMPs are heat shock proteins (HSP), monosodium urate, high mobility group box protein 1 (HMGB1), and nucleic acids including extracellular ATP and mitochondrial DNA. Inflammatory cytokines such as IL-1a and IL-33 can also act as DAMPs and are passively released from necrotic cells.

Molecular danger signals and destruction of local barriers are detected by the complement and coagulation systems. Intracellular signal transduction is induced in leukocytes via PRRs. As a result, a rapid cellular immune response is triggered. All of these trigger the formation of more DAMPs and PAMPs and put nonspecific immune responses in a vicious circle. That plays a crucial role in controlling the immune system balance during the acute phase.

In surgical traumas, DAMPs have similar properties to PAMPs, such as signaling through receptors and containing comparable molecules and components.

The increase in DAMP, HMGB-1 and IL-6 levels in mononuclear cells in the perioperative region indicates that inflammation is triggered in the body. Especially HMGB-1 is specifically secreted in patients with surgical trauma. Additionally, parts of ECM components such as hyaluronic acid, collagen, elastin, fibronectin, and laminin all stimulate inflammation.

1.3. Toll-Like Receptors

The danger signals triggered by tissue damage after implantation, vary according to the death pattern of the cells in the tissue and the extent and location of the tissue damage.

TLRs and IL-1R1 have been shown to negatively affect the repair of various tissues. Overall, it is clear that danger signals significantly influence the healing process in the early stages.

Toll-like receptors (TLRs) and other PRRs recognize danger signals and trigger inflammation through the activation of transcription factors such as NF-kB (Nuclear Factor-kappa B) or interferon regulatory factors.

TLRs activate the expression of the chemoattractants for macrophages, neutrophils, and monocytes as well as macrophages found in tissue. They also induce the expression of proinflammatory cytokines such as TNF-α, IL-1β, and IL-6.

Inflammation in response to necrotic cells is mostly mediated by the IL-1 receptor (IL-1R), resulting in NF-kβ activation. IL-33 acts as a primary danger signal via the ST2 receptor.

In humans, the TLR family has 13 members. They are divided into two subfamilies, cell surface, and intracellular TLRs, according to their localization. Cell surface TLRs: TLR1, TLR2, TLR4, TLR5, TLR6, and TLR10. Intracellular TLRs: TLR3, TLR7, TLR8, TLR9, TLR11, TLR12, and TLR13. The intracellular TLRs are localized in the endosome. Cell surface TLRs mainly recognize microbial membrane components such as lipids, lipoproteins, and proteins.

TLR4 is a transmembrane signaling receptor associated with the innate immune system and the specific immune system. In particular, the integration of TLR4 ligand with lipopolysaccharide (LPS) activates two intracellular pathways: MyD88-dependent and MyD88-independent pathways.

With TLR4 binding to its ligand, NF-κB is activated. TLRs recognize DAMPs, trigger the downstream signaling pathway, and activate transcription factors. In this way, they induce the development and progression of inflammation. Studies have shown that it is mainly mediated by TLR4-MyD88/NF-κB-dependent complex signaling, especially in tissue damage and surgical trauma.

The innate immune system uses PRRs for the initial detection of inflammatory agents. PRRs recognize PAMPs and self-generated DAMP molecules from damaged cells after implantation. PRRs activate innate immune responses by producing type I IFN and inflammatory cytokines. In this process, both the host's defense mechanisms, such as inflammation, are triggered, and antigen-specific adaptive immune responses are regulated. These responses are important in the suppression of inflammation and also in the generation of specific immune responses.

Each TLR contains the LRR that enables PAMP recognition and the cytoplasmic Toll/IL-1 receptor (TIR) that initiates downstream signaling. After recognition of PAMPs and DAMPs, TLRs bind to TIR domain-containing adapter proteins such as MyD88 and TRIF. This connection is mediated by the activation of type I IFNs, NF-κB, interferon regulatory factor (IRF),

and mitogen-activated protein kinases (MAPK) that protect the host from inflammation.

All TLRs are synthesized in the endoplasmic reticulum (ER), transferred to the Golgi apparatus, and recruited to the cell surface or intracellular compartments such as endosomes. Intracellular localization of TLRs is critical for ligand recognition. TLRs bind differently to adapter members containing TIR domains, such as MyD88, TRIF, TIRAP/MAL, or TRAM. While this interaction induces different pathways after surgical trauma, also causes suppression of some physiologically activated pathways.

Physiologically, MyD88 is used by all TLRs and activates NF-κB and MAPKs to stimulate inflammatory cytokine genes. TIRAP is an adapter that binds MyD88 with cell surface TLRs such as TLR2 and TLR4. TIRAP has also been shown to be involved in signaling via endosomal TLRs such as TLR9. TRIF merges with TLR3 and TLR4 to stimulate an alternative pathway. This pathway leads to the activation of IRF3, NF-κB, and MAPKs for the stimulation of type I IFN and inflammatory cytokine genes. On the other hand, TRAM merges with TLR4 to bind TRIF to TLR4. TLR3 interacts directly with TRIF. Overall, based on the adapter usage, TLR signaling is largely split into two pathways: MyD88-dependent and TRIF-dependent pathways.

In recent years, studies have been accelerated to explain the above pathways more clearly. Accordingly, it has been shown that both MyD88-dependent and MyD88-independent pathways play an important role in the activation of TLR-4. The absence of a molecule in these pathways or changes in the activity of each molecule can lead to different responses.

In MyD88 and MyD88-like adapter pathways, NF-κB passes into the nucleus and dissociates from the inhibitory protein (I-κB) to which it is bound. It causes the upregulation of genes for inflammation, secretion of some proinflammatory cytokines, and stimulation of the specific immune system. There are 5 different NF-κB proteins known as RelA (p65), RelB, c-Rel, NF-κB1 (p50/p105), and NF-κB2 (p52/p100). For optimal immune responses, the proper regulation of CD4+ CD25+ Treg cells is critical.

Akyol, S. et al. (2020) investigated the effect of titanium alloy (Ti) and stainless steel (SS) implants on immunological responses, a comparative analysis of NF-κB profiles in the activation of inflammatory signaling pathways, and the role of CD4+/CD25+/Foxp3+ (Tregs). The immune responses to Ti and SS alloy in the acute and chronic stages after implantation are schematically given in *Figure 2*.

It has been shown that active acute phase responses are intense until day 7, the transition from the acute period to the chronic period is between days 7 and 14, and chronic responses are received between days 15 and 28 after implantation of SS and Ti alloys. According to the results of the study, the connective tissue reconstructs the traumatic area, in the post-implantation chronic inflammation phase.

This study showed that the first line of defense against Ti and SS alloy after implantation is provided by the innate immune mechanism, and this mechanism triggers specific immune responses. It has been emphasized that different immune responses occur against different biomaterials. TLRs are the molecules that constitute the first response to implant materials. These receptors recognize individual PAMPs expressed on infectious agents. With the activation of these receptors, NF-κB is stimulated and several inflammatory target genes are activated.

LPSs are potent stimulators of the innate immune system and its most important ligand is TLR-4. To generate an activation signal in the cell, LPS and CD14 form a complex and this complex interacts with TLR-4. It was reported that the CD14 level in the SS alloy group was lower than the control and Ti alloy groups from the 7th to the 28th day after implantation. Compared with the control group, the CD14 level in the Ti alloy group did not change significantly. CD14 causes LPS binding to TLR-4 followed by activation of the TLR-4 pathway.

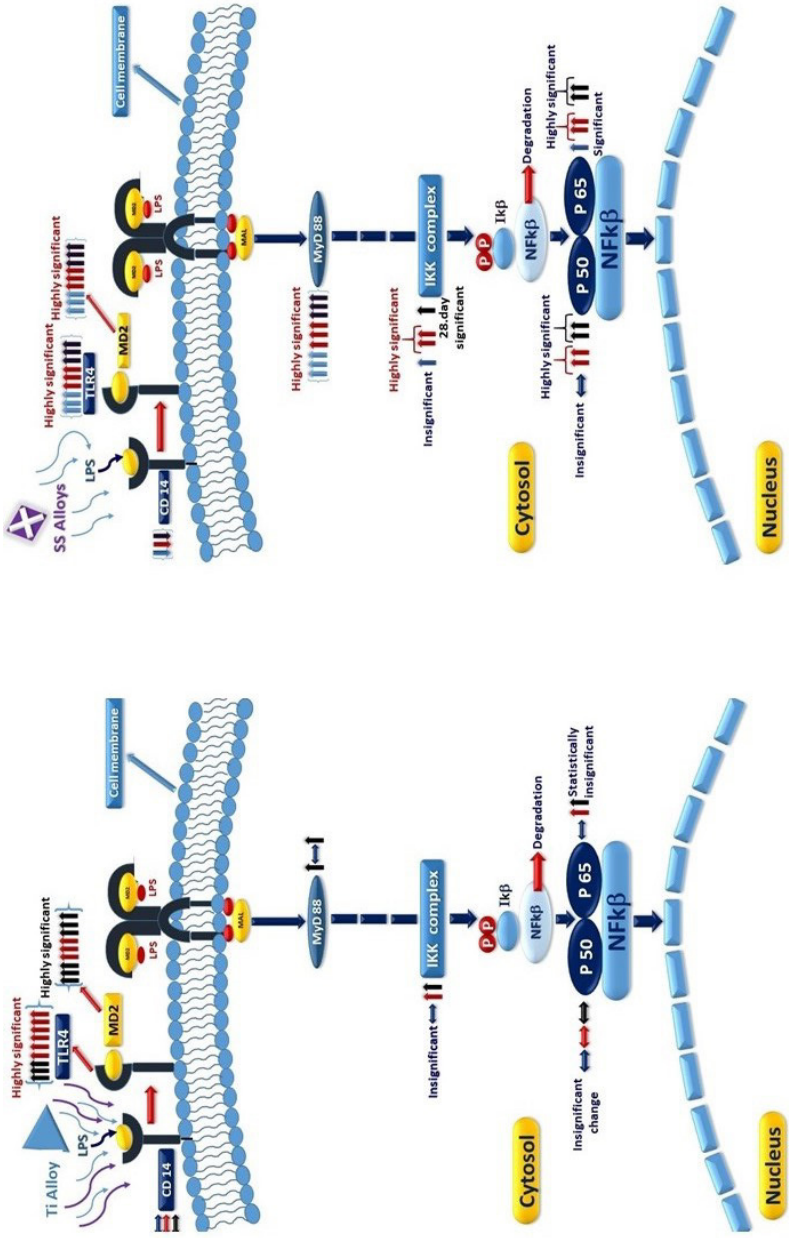

Figure 2. CD: cluster of differentiation, IKK: inhibitor of κB kinase, LPS: lipopolysaccharide, MD2: myeloid differential protein-2, MyD88: myeloid differentiation primary response 88, NF-κB: nuclear factor kappa B, SS: stainless steel, Ti: titanium, TLR: toll-like receptor. (From *Akyol S, et al. Comparative Analysis of NF-κB in the MyD88-Mediated Pathway After Implantation of Titanium Alloy and Stainless Steel and the Role of Regulatory T Cells; 2020.*)

Recent studies suggest that LPS triggers immune responses and is required to form the LPS and CD14 complex. Stimulation occurs without the need for LPS stimulation after the implantation of biomaterials. Direct stimulation takes less time than LPS stimulation. Therefore, the change in CD14 level is not primarily important in triggering the cascade.

In the study, MD2 and TLR-4 expression in the SS alloy group showed statistically significant increases on all days compared to the Ti alloy group. TLR-4 and its ligands go through the MyD88-dependent pathway and trigger cellular activation. MyD88 was significantly increased in the SS group on all days. TLR-4, MD2, and MyD88 levels were lower in the Ti group compared to the SS group on all days. The very significant increase in MyD88 in the SS alloy group compared to the Ti alloy group is critical for both TLR-stimulated signaling and induction of NF-κB activation. It is effective in the regulation of inflammation.

On day 14, there was a significant increase in IKK (inhibitor of κB kinase) levels in the SS group, leading to the activation of inflammatory cytokines.

P50 and RelA/p65 are present in the cytoplasm and nucleus during NF-κB activation. P50 is the target molecule. The significant increase in RelA/p65 level from the 7th day to the 28th day in the SS alloy group indicates that the activation of NF-κB increased in this group. The increase in IKK, p50, and RelA/p65 levels in the Ti group indicates NF-kB activation. Activation of this pathway is seen in the innate immune response and prevention of apoptosis in different conditions.

TLR signals directly or indirectly regulate CD4+/CD25+ Treg cell activities, creating an immune response against self-antigens or non-self-antigens in implant rejection, infectious diseases, and immune suppression. The decrease in Treg cells in the SS group may trigger the cytotoxic and suppressive immune response and lead to the onset of pathological damage. It has been shown that Ti implants cause an increase in Treg levels and control the destructive immune response.

1.4. Inflammatory Cells

Neutrophils are the first inflammatory defense cells to arrive at the site of injury after implantation and their numbers increase at the wound site for defense. Neutrophils have anti-inflammatory properties. Tightly controlling neutrophil mobilization and function promotes tissue repair and regeneration.

A high number of mast cells is detrimental to tissue regeneration. Mast cells expand the acute inflammation and cause scarring in the central nervous system, and their number is high after implantation.

Macrophages are involved in the development of organs, the functioning of tissues, tissue regeneration, and the regular release of growth factors and matrix components. Macrophages are an important source of various proteases, cytokines, growth factors, ECM components, and soluble mediators that promote tissue repair, fibrosis, or regeneration.

Macrophages arrive at the implantation site 1-3 days after neutrophils. They reach the maximal level after 4-7 days. However, they are seen at the implantation site up to day 21.

Macrophages form M1 (classical activation, proinflammatory) and M2 (alternative activation, anti-inflammatory) polarization patterns. M1 macrophages called pro-inflammatory macrophages can alternatively polarize into activated anti-inflammatory M2 macrophages. In vitro studies have shown that M1 is formed with the stimulation of IFN-γ and TNF-α and M2 is formed by IL-4 and IL-13 stimulation.

M (IL-4) macrophages form tissue-repairing macrophages by expressing arginase, ECM components, and different wound healing factors such as VEGF-A, PDGF, and insulin-like growth factors (IGF).

Inflammatory macrophages exacerbate tissue damage and inhibit tissue healing during the post-implantation period. The sustained mobilization of M (IL-4) macrophages causes the development of pathological fibrosis and they produce significant amounts of matrix metalloproteinase (MMP). Macrophages are also anti-inflammatory and anti-fibrotic. They are thought to be important in tissue healing in post-implantation inflammatory responses.

M1 activation is induced by intracellular pathogens, bacterial cell wall components, lipoproteins, and cytokines such as IFN-γ and TNF-α. M1 macrophages are observed during the acute response to the trauma and release high levels of reactive oxygen species (ROS). They have an effective pathogen-killing mechanism (microbicidal), characterized by inflammatory cytokine secretion and nitric oxide (NO) production. They increase the efficiency of innate immune defense by increasing proinflammatory cytokine (IL-1β, TNF-α, IL-8, IL-12, IL-18) release and phagocytosis, removing pathogens and wound debris from the wound area.

M2 activation is triggered by fungal cells, parasites, immune complexes, complement products, apoptotic cells, macrophage-colony stimulating factor

(M-CSF), IL-4, IL-13, IL-10, and transforming growth factor-β (TGF-β). They produce IL-10, IL-12, ECM components, and angiogenic and chemotactic factors and have high phagocytosis capacity. They also play a role in the clearance of apoptotic cells, reducing the inflammatory response and promoting wound healing.

M2 macrophages can cause allergic inflammation and the growth of tumor tissues. In humans and rodents, GM-CSF (Granulocyte-macrophage colony-stimulating factor) induces differentiation into M1 macrophages, while M-CSF initiates M2 production in macrophages.

M1 macrophages express the markers CCL3, CCL4, MHC II, CD68, CD80, and CD86 on their surface. When activated, they secrete the chemokines CXCL9 and CLXCL10, which stimulate the Th (helper) 1 cell response. They support the Th1 immune response as a result of the production of highly reactive nitrogen and oxygen intermediates.

Since M2 macrophages are in different activation states functionally, they encompass various groups. Accordingly, M2 macrophages are specifically classified into M2a, M2b, and M2c subgroups based on their distinct gene expression profiles, activation signals, cell surface receptors, and functional diversity. All subtypes of the M2 macrophages are evenly immunosuppressive. In the studies, different macrophage subgroups such as M2d, M4, Mox, and Mha were also reported. M2 macrophages with high plasticity are capable of transforming into all M2 subtypes.

IL-10, an immunoregulatory cytokine produced by macrophages, Th2, and regulatory T (Treg) cells, is an important anti-inflammatory mediator. Anti-inflammatory macrophages regulate the development and maintenance of Tregs that produce IL-10 and TGF-β1, thus they contribute to the healing of inflammation in many tissues.

In recent years, it has been shown that macrophages are important in tissue regeneration and restoration after surgical trauma.

1.4.1. Important Macrophage Markers Activated After Implantation

Macrophage inflammatory protein 1-α (MIP-1-α), also known as CCL3, membrane protein, by binding to the CCR1 receptor plays a role in acute inflammatory responses and the recruitment processes and activation of polymorphonuclear leukocytes. CCL3 causes monophasic fever in the inflammatory process with TNF-α and IL-1 stimulation. A study suggests that CCL3 is produced locally in response to post-implantation infection. CCL3 is

also involved in the host response during acute or chronic phases of infection. CCL3 is produced by endothelial cells, fibroblasts, neural tissue, and various tumor cells as well as monocytes, macrophages, and neutrophils. Macrophage Inflammatory Proteins (MIP(CCL3)) participate in osteoclast formation, providing a link between local inflammation and bone resorption leading to the loosening of the implant.

CCL4 (MIP-1β) is a protein encoded by the CCL4 gene in humans. MIP-1β is produced by macrophages and monocytes after stimulation with bacterial endotoxin or IL-1β. It is produced by all hematopoietic cells and fibroblasts, epithelial cells, vascular smooth muscle cells, or platelets after stimulation with the inflammatory agent.

They are important in the development of an immune response against infection and inflammation. Their action is mediated by binding of the chemokine receptors CCR1 (ligand CCL3) and CCR5 (ligands CCL3 and CCL4). The signal is then transferred to the cell. In this way, these cytokines affect any cell that possesses these receptors. The major effect is inflammatory and consists mainly of chemotaxis and transendothelial migration. However, cells can also be activated to release certain bioactive molecules. These chemokines affect monocytes, T lymphocytes, dendritic cells, NK cells, and platelets. These, in turn, activate human granulocytes, which can lead to acute neutrophilic inflammation. They also induce the synthesis and release of other proinflammatory cytokines such as IL-1, IL-6, and TNF-α from fibroblasts and macrophages.

CD163 is a membrane protein. It has high expression in tissue macrophages such as red pulp macrophages, bone marrow macrophages, liver macrophages (Kupffer cells), and lung macrophages, however, its expression is limited in the monocyte-macrophage line. The most potent stimulators of CD163 expression are glucocorticoid, IL-6, IL-10, and heme/hemoglobin (Hb). IL-4, LPS, TNF-α and IFN-γ, CXCL4, and GM-CSF decrease its expression.

It has been reported that CD163 is found on the surface of M2 macrophages. Macrophages co-expressing CD206 and CD163 produce high levels of IL-10, IL-1 receptor antagonist (IL-1RA), and CCL18.

The mannose receptor CD206 is found primarily on the membrane surface of macrophages, secondarily on immature dendritic cells. Humans express two types of mannose receptors, each encoded by its own gene: Macrophage mannose receptor C type 1 (with MRC1 gene, CD206) and Macrophage mannose receptor C type 2 (with MRC2 gene, CD280). They can recognize microbial carbohydrates and mediate phagocytosis. CD206 is found in cells that form barriers (such as

keratinocytes, lymphatic and hepatic epithelium, kidney mesenchymal cells, tracheal smooth muscle, and retinal pigment epithelium) and antigen-presenting cells (such as macrophages, dendritic cells derived from human monocytes, and some subpopulations of mouse dendritic cells). Functionally, CD206 is active in antigen processing, endocytosis, and phagocytosis, which play an essential role in the innate immune response. CD206, also called MRC1, is an M2 macrophage marker in both mice and humans. Moreover, the absence of CD206 causes elevated serum levels of inflammatory proteins and the resolution of inflammation. However, CD206-expressing macrophages have adverse profibrotic effects, as they promote fibroblast growth by TGF-β and CCL18 secretion.

CCL1 is a small glycoprotein, known as a chemokine that belongs to a family of inflammatory cytokines, secreted by activated T cells, monocytes, and mast cells. CCL1 interacts with the CCR8 ligand, attracting monocytes, NK cells, immature B cells, and dendritic cells toward the site of inflammation. CCL1 acts as a chemotactic for macrophages.

The Signaling Lymphocytic Activation Molecule (SLAM/CD150) is a self-ligand glycoprotein encoded by the SLAMF1 gene. SLAM is found on the surface of activated T cells, memory T cells, activated B cells dendritic cells, and macrophages. It also plays an important role in adhesion between T cells and antigen-presenting cells.

Similar to macrophages, dendritic cells (DCs) phagocytize foreign particles in the tissue and direct danger signals at the site of post-implantation damage. They play an important role in tissue repair and regeneration as well as tissue healing. For example, plasmacyte DCs have been shown to sense skin injury via TLR7 and TLR9 and promote wound healing with type I interferons. DCs act as immune regulators during the process of tissue healing through the control of macrophage homeostasis.

Recent studies have shown that T cells play an important role in tissue repair and regeneration. Interesting mechanisms are emerging at the implantation of surgical biomaterials. The function of different T cell types and subgroups and their accumulation levels at injury sites are not clearly known. It is also known to show different functional properties in different tissues. α-βT cell fractions have both pro- and anti-regenerative subgroups.

Meanwhile, the permanent gamma/sigma Tcell fraction of the tissue is pro-regenerative. T cells co-secret stimulatory or inhibitory cytokines and growth factors during the process of tissue healing.

Some studies in humans have shown that the release of IFN-g and TNF-a by effector memory CD8+ T cells results in delayed osteogenesis and fracture healing. On the other hand, some studies have shown that CD4+ Tregs are critical for the repair and regeneration of many tissues. For example, following spinal injury in mice, Tregs accounted for 50% of the T cell population on days 14 and 30. D4+CD25+ Treg cells are a lineage of CD4+ T cells characterized by Forkhead box P3 (Foxp3) factor expression and TGF-β production.

Treg cells, secreting inhibitory cytokines such as IL-10, TGF-β, and IL-35 and interacting directly with the cell, act as immunosuppressive. IL-10 inhibits Th1 and Th2 cell responses by means of antigen-presenting cells. It has also been reported that IL-10 can inhibit the initiation of Th17 cell response but has no suppressive effect on Th17 cell-mediated chronic inflammation.

These secreted cytokines provide a favorable anti-inflammatory microenvironment for macrophage repair and polarization. α-βT cells are also important in the process of tissue healing. For example, in both humans and mice, traumatic wounds do not heal quickly or effectively in the absence of α-βT cells.

Functionally, during the process of traumatic tissue repair, insulin-like growth factor-1 (IGF-1) is released by both mouse and human gamma/sigma T cells.

In the context of tissue healing, dendritic epithelial ɣdT cells (DETC) are known as the best-characterized cd subset. In general, ɣd T cells play an important role in promoting both innate immune cells and direct tissue growth. Treg and ɣdT cells secrete growth factors and cytokines that play an important role in the repair of traumatic tissue. However, the mechanisms of immune response regulation of different T cell types and their subgroups against tissue injury are not fully defined. However, T cells probably interact directly with stem or progenitor cell populations present in the tissue.

There is little evidence on the role of B cells in tissue healing. Given the origin of B cells in the bone marrow, it is conceivable that there is a cross talk relationship between B cells and bone tissue. For example, IgM+B cells play an important role in repair by secreting osteoprotegerin to accelerate bone regeneration.

Interestingly, CD4+ T cells help upregulate osteoprotegerin via the CD40/CD40L pathway, while CD8+ T cells inhibit osteoprotegerin expression.

Akyol S. and et al. investigated the immunological changes in peripheral blood after implantation of SS alloy and Ti alloy by analyzing CD4, CD8, CD25

(IL-2R) CD4+CD8+ (lymphocyte gate), CD4+CD25+Foxp3+ (Tregs), and anti-inflammatory (IL-4, IL-10, IL-6) and proinflammatory (IL-17A, TNF-α, TGF-β) cytokines.

The altered immune mechanisms after implantation are shown in *Figure 3*.

Antibody-dependent immune response, and activates the mechanism by triggering the development of immune tolerance and inhibiting the occurrence of immune response-related damage.

2. Immune Modulation by Physico-Chemical Properties of Biomaterials

According to their physicochemical properties, biomaterials play an active role in the immune system and macrophage polarization which stimulate or suppress inflammation.

The shape of the biomaterial (solid, hydrogel, or micro/nanoparticles), cross-linking and hydrophobicity properties, biodegradability and biotolerability levels, topography, and the pore size and surface structure of the biomaterial are all effective factors in implantation.

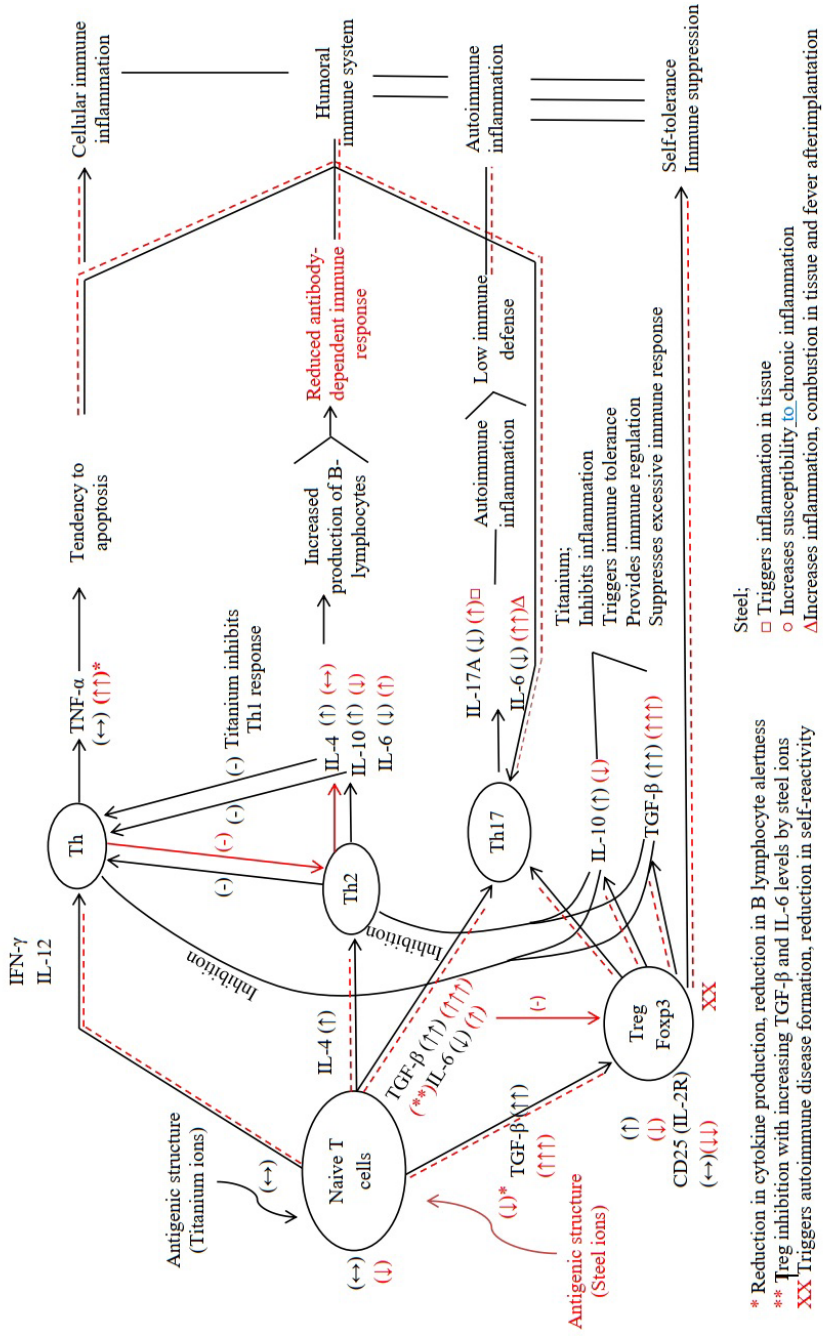

Figure 3. (From Akyol S, et al. Which is Better: Stainless Steel or Titanium Alloy?, 2018.)

As a result of the study, it was shown that Ti aloy, unlike SS, suppresses the development of inflammation by inhibiting the proinflammatory response, strengthens the humoral immune system by enhancing the

Natural biomaterials are tissue scaffolds made of natural molecules such as collagen or decellularized tissues (like human or porcine skin or small intestinal submucosa (SIS)), fibrin, hyaluronic acid, chitosan, alginate, or silk.

The surface chemistry of implant materials affects macrophage adhesion and cytokine secretion profile. For example, neutrally charged hydrophilic modified polymers have been shown to stimulate macrophages and giant cells less than hydrophobic and ionic surfaces.

Although the amount of cells having hydrophilic/neutral surfaces, macrophages produce much higher amounts of cytokines (IL-1, IL-6, IL-8, and IL-10) compared to hydrophobic and ionic surfaces.

Biomaterials of natural origin such as high molecular weight hyaluronic acid and chitosan have anti-inflammatory properties.

In order to control the inflammatory microenvironment in the implantation of biomaterials, anti-inflammatory cytokine activation must be stimulated. Natural biomaterials, such as collagen and fibrin, release immune modulators upon enzyme-mediated degradation.

Synthetic materials, when implanted, enhance the kinetics of degradation and release of therapeutics through stimulation.

2.1. Immune Modulation by Decellularized ECM

Cells detach from the extracellular matrix, and only the decellular ECM tissue scaffold remains. These natural tissue scaffolds influence the cellular process and are used to create a pro-regenerative environment. Since ECM proteins are highly conserved across species, xenografts are generally well tolerated. Regulation of the immune environment limits the risk of unwanted inflammation.

Among other properties, the decellularized ECM modulates the immune microenvironment at the wound site through macrophage polarization by directing macrophages to either an M (IFN-γ) or M (IL-4) phenotype. This immune modulation often shows differences depending on the composition and structure of the tissue scaffold.

2.2. Release of Inflammatory Molecules

Great emphasis is placed on tissue repair rapidly in a short while by reducing undesirable inflammatory responses after implantation. However,

pro-inflammatory molecules are essential for the initiation of tissue healing. Some studies have shown that the administration of heat shock protein 70, an endogenous agonist of TLR2 and TLR4, accelerates wound healing by up-regulating macrophage-mediated phagocytosis.

2.2.1. SDF-1

SDF-1 is an important inflammatory and pro-angiogenic chemokine, particularly in the tissue healing process with its ability to mobilize progenitor cells.

Biomaterials providing SDF-1 have been used for many tissue types and their beneficial effect has been demonstrated in tendon, heart muscle, skin, and liver models.

2.2.2. PGE2

Prostaglandin E2 (PGE2) is part of the proinflammatory lipid molecules known as prostanoids. PGE2 and its multiple receptors (EP1, EP2, EP3, and EP4) carry out both pro- and anti-regenerative functions.

PGE2 has the ability to enhance bone formation and angiogenesis. It is therefore actively released after implantation. Within the immune system, PGE2 induces the proliferation of T and causes their apoptosis.

PGE2, although pro-inflammatory, is known to inhibit proliferation and influence the immune response towards Th2, inhibiting IL-12, IFN-γ, and IL-2 secretion by lymphocytes. Although PGE2 is beneficial in tissue healing, different doses of PGE2 are used in treatment. The use of PGE2 in high doses weakens the effectiveness of the therapy as it causes strong side effects.

2.3. Release of Anti-Inflammatory Molecules

Inflammation at the implantation site is necessary to initiate the healing response. The initiation of this response accelerates the healing process. The initiation of this response is important for tissue repair. The anti-inflammatory function of macrophages is important in the early period. However, macrophages play an active role in tissue healing by polarizing towards an anti-inflammatory phenotype. Macrophages perform the pro-resolving activity by stimulating the formation of Tregs. Tregs stimulate the anti-inflammatory properties of macrophages and play role in tissue repair. Mechanisms naturally exist to induce the transition from a pro-inflammatory phase to a state of resolution.

Therapeutic strategies supporting this transition can accelerate the healing process.

2.3.1. TNF-α Inhibitors

TNF-α stimulates the pro-inflammatory activity of M(IFN-γ) macrophages. TNF-α regulates tissue repair and regeneration, and its excessive secretion impairs and delays the healing process. For example, pathological levels of TNF-α may induce osteoclastogenesis, resulting in greater bone absorption than osteogenesis. Local administration of painkillers such as aspirin, ibuprofen, and pentoxifylline are effective in reducing TNF-α. For example, local delivery of aspirin with hydroxyapatite/tricalcium phosphate ceramic particles reduces TNF-α and prevents apoptosis of MSCs, resulting in more bone regeneration.

2.3.2. Inhibitors of the NF-κβ Pathway

NF-κB activity triggers by inflammatory cytokines such as TNFα, IL-1, bacterial cell wall components like lipopolysaccharides, viruses and physical stress conditions such as UV radiation. Blocking NF-κB signaling compromises immune response formation.

Many factors like infection, stress and trauma damage the body. Systemic administration of NF-κB inhibitors can therefore impair immune function. However, inhibition of NF-ƙβ sometimes accelerates the healing of some tissues.

2.3.3. Anti-Inflammatory Cytokines

Anti-inflammatory cytokines such as IL-4 and IL-10 are effective in tissue repair and regeneration. They play role in the conversion of M (IFN-ɣ) to M (IL-4) macrophages.

Another anti-inflammatory cytokine is TGF-β1, which is essential for tissue repair at the earliest stage. TGF-β shows pro-inflammatory or anti-inflammatory effects depending on the type of incoming stimulus. TGF-β suppresses lymphocyte proliferation and activity. It induces Tregs.

This cytokine is highly active in scar formation. However, there are three isoforms of TGF-β (TGF-β 1, 2 and 3). TGF-β3 accelerates regeneration and prevents scar formation. When TGF-β3 alone was injected into incisional wounds, it was observed to reduce postoperative scarring.

3. Recovery after Trauma and Implantation

The healing process after surgical trauma is divided into three phases: inflammation phase, proliferation phase and remodeling phase. These phases may vary according to factors such as the age and health status of the individual, the severity of the injury, and the type of injured tissue. In general, the inflammatory phase lasts for 1-2 days. The proliferation phase that starts afterward peaks in about 1 week. The remodeling phase that starts during the proliferation phase continues until tissue integrity is restored and may last for months.

Different macrophage subtypes are involved in different stages of the healing process. While M1 macrophage activation is seen in the proinflammatory acute phase, M2 macrophages are activated in the following process. The synergistic action of M1 and M2 macrophages, as described above, results in successful wound healing.

There are differences between the repair systems of traumatic areas taking place in the wake of surgical trauma. To compare these differences, in vitro studies using macrophage phenotypes have demonstrated that wound repair takes place mediated by M1-M2c macrophage activation.

Accordingly, both M1 and M2c macrophages are involved in the inflammatory phase. Proinflammatory cytokine release lasts in the early proliferative phase, but there is a shift towards anti-inflammatory cytokines such as IL-10. During these changes, macrophages in the proliferative phase transform into the M2b phenotype.

In the late proliferative phases, M2c macrophages are stimulated by IL-10 and TGF- β expression. Decreased levels of Arginase-1 and increased expression of CD206 and TGF- β in the remodeling phase indicate that M2c is the dominant phenotype in this phase.

At the end of the remodeling phase, macrophages are deactivated. If wound repair is successfully completed, macrophage numbers return to normal levels within weeks. Wounds that do not heal within three months are considered chronic and persistent macrophage activation is an important indicator of this condition. The sustained and false activation of macrophages disrupts the stages of repair.

3.1. Inflammatory Phase

It starts with tissue damage and is the first stage of tissue repair. With the onset of the inflammatory cascade after trauma, the migration of inflammatory

cells into the tissue begins. Usually, within a day, neutrophil accumulation reaches a peak level.

Macrophages in this phase, 1) Similar to M1 cells stimulated in vitro, they express high levels of TNF-α, IL-1β, IL-6, and IL-12, 2) They express high levels of arginase and Ym1, which is indicative of M2a macrophage activation.

M1 and M2a macrophages are involved in the inflammatory phase of surgical wound repair. M1 macrophages secrete proinflammatory cytokines, attract neutrophils to the site and increase the inflammatory response. M2a macrophages initiate the proliferative phase with the release of anti-inflammatory cytokines. IL-4, CD206, and Fizz-1 expression reach maximum level along with arginase expression within 1-3 days after injury.

3.2. Proliferation Phase

In the proliferation phase of tissue repair after surgical trauma, proliferation begins around day 2, peaks around day 5 and regresses on days 10-12.

Endothelial cells and fibroblast-lineage cells migrate to the site of inflammation and restore tissue integrity and barrier functions. During the proliferation phase, angiogenesis, tissue granulation, collagen deposition, and ECM formation occur. Unlike the inflammatory phase, macrophages in this phase are of the M2b subtype and secrete IL-10.

In this phase, macrophages are involved in the maturation of proliferating cells and the stabilization of damaged tissue.

Macrophages; 1) facilitate cell proliferation in the late inflammatory phase, 2) sustains proliferation in the proliferative phase, and 3) cause the maturation of cells to initiate the remodeling phase.

In the transition to the remodeling phase, proinflammatory (IL-12) cytokine release decreases while the expression of anti-inflammatory cytokines and growth factors (IL-10, TGF-β, IGF-1) increases.

3.3. Remodelling Phase

It is the last phase of traumatic wound healing. It starts 2-3 weeks after trauma and continues for months. Cells that have proliferated in the proliferation phase mature in this phase. Inflammation, scar formation, and angiogenesis that started in previous phases slow down and stop.

Growth factors such as PDGF, TGF-β, FGF, and matrix metalloproteinases (MMP) strengthen the tissue by regulating the remodeling phase. At the end of the remodeling phase, complete wound repair occurs. The dominant macrophage

subtype in this phase is M2c. Decreased M2a and M2b macrophage markers (VEGF, Arginase-1, IGF-1) and increased expression of CD206, CD163, and TGF-β are used as indicators of this condition. In the remodeling phase, macrophages contribute mainly through their inhibition. When inhibition does not occur, the continuance of the presence of proinflammatory macrophages is associated with chronic wound formation.

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CHAPTER III

EFFECT OF SURGICAL INNOVATIONS ON PATHOLOGY ROUTINE

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1. Introduction

Pathology is the study of the causes, effects, and nature of diseases. It involves examining tissues, cells, and organs to diagnose and determine the cause of a disease. Pathologists also study the response of the body to treatment for a disease.

Pathology as a scientific discipline began in the 18th century with the work of Italian anatomist and physician Giovanni Battista Morgagni. He was the first to systematically study and describe the anatomy of diseased organs. Later in the 19th century, German pathologist Rudolf Virchow developed the cell theory, which helped form the basis of modern pathology.

A biopsy involves taking a small sample of tissue from the affected area. The sample is then examined under a microscope to check for any abnormal cells or other signs of disease. The sample may be taken using a needle, during surgery, or through a biopsy punch. The tissue sample is typically sent to a laboratory for further testing and analysis.

With the development of technology, smaller tissue samples can be taken from deeper organs. The development of anesthesia technologies has also allowed longer surgeries can be performed. This brought along the demand that some decisions made during the surgery be made with the support of pathology evaluation. Another development is the increase in the variety of interventional and medical treatments that can be applied before surgery. This situation causes various changes in the organ.

There are several types of biopsies, each of which is used to diagnose different conditions. These include:

- Needle/core biopsy: This is the most common type of biopsy and is used to collect a small sample of tissue. It can be used to diagnose cancer, infections, or other abnormal conditions.

- Excisional biopsy: This type of biopsy involves surgically removing a larger piece of tissue in order to diagnose cancer, infections, or other abnormal conditions.

- Aspiration biopsy: This type of biopsy is used to collect cells from a suspicious area. It can be used to diagnose cancer, infections, or other abnormal conditions.

- Endoscopic biopsy: This type of biopsy is used to examine and collect tissue samples from the lining of organs, such as the stomach or intestines. It can be used to diagnose cancer, infections, or other abnormal conditions.

2. Changes Due To The Reduction In The Size Of The Biopsies

Technological developments in biopsy procedures have allowed for smaller biopsy samples to be taken, which has improved the accuracy of diagnoses. As technology has advanced, biopsy procedures have become less invasive, allowing for smaller sample sizes to be taken with less patient discomfort. This has allowed for more precise and accurate diagnoses, while also reducing the risks associated with biopsy procedures.

With the endoscopic procedures and needle biopsies, it has become possible to obtain very small tissue from many organs (Picture 1). This change brought with it the necessity of being very careful during macroscopic examination and sectioning. In the slightest distraction, there is a risk of the tissue ending. In addition, since tissues of these sizes cannot be distinguished from each other macroscopically, care should be taken to avoid confusion, and it should be ensured that the barcodes on the tissue containers and the identification information on the prompts match.

Picture 1. Size endoscopic biopsy

Biopsies of different sizes also necessitated the creation of biopsy cups of different sizes. Biopsy containers should be of various sizes depending on the size of the sample that needs to be taken. Smaller samples require smaller containers, while larger samples require larger containers. In addition, the type of biopsy performed can also determine the size of the container needed.

3. Increased Expectations For Intraoperative Evaluation And Limitations Of This Method

Intraoperative pathologic evaluation is a type of biopsy which is conducted during a surgical procedure. During the procedure, a pathologist examines tissue samples taken from the patient to diagnose and determine the cause of a disease. This type of biopsy is beneficial as it can provide immediate information to the surgeon regarding the patient's condition and help inform decisions regarding the best course of treatment.

With the development of technology and the prolongation of anesthesia times, the necessary conditions for intraoperative diagnosis have been created. At the beginning of the 20th century, this method began to be developed further and became an integral part of surgery. During this method, tissue is frozen and sections are taken (Picture 2).

Picture 2. Freezing and sectioning of tissue during intraoperative evaluation

Diagnoses are sometimes limited in intraoperative evaluation due to artifacts and the inability to apply histochemical/immunohistochemical methods. In some cases, even the malignant-benign distinction cannot be made clearly. To prevent this situation, diagnostic possibilities and what to do in these cases should be determined in advance in clinicopathological meetings before the operation.

While this method is convenient, it comes with some disadvantages. The most obvious disadvantages are the inability to obtain quality images as in paraffin-embedded tissues and the inability to study immunohistochemical methods in frozen sections. The artifacts that cause the image to be of poorer quality are listed below:

Ice crystal artifacts

It is caused by slow freezing. Freezing should be provided as quickly as possible. Reduction of adipose tissue can prevent this artifact.

Blade artifacts

The blades may be damaged or not fixed on the microtome. Sections appear wavy.

Painting defects

In general, paints and liquids can become dirty quickly, after fast and pourable sections are painted. Routine checks and renewings are required.

Air bubbles

It is caused by the presence of air under the lamella. It should be removed as it will cause the underlying tissue to dry out.

Fatty tissues

Fat tissues are tissues that are very difficult to cut compared to other tissues. It occurs in tissues such as breast, skin, lymph nodes. It should be frozen at -20°C and below temperature values.

4. Increased Expectations From Pathological Evaluation

4.1. Difficulties In Identifying The Tumor

One of the main difficulties in identifying the tumor in pathologic evaluation is the fact that the sample taken may not be representative of the entire tumor. The sample may be too small, or the tumor may have spread to other parts of the body, making it difficult to accurately diagnose the nature of the tumor. Additionally, there may be difficulty in distinguishing between benign and malignant tumors, as they may look similar under a microscope. Although some tumors show very small differences morphologically, differential diagnosis can be made by immunohistochemical methods. However, immunohistochemistry requires time and is not possible during intraoperative evaluation. Therefore, in some cases, it is stated that only the general title interpretation is made and further examinations will be made after embedding in paraffin. In the periods when molecular evaluations could not be made, the diseases mentioned under the same title are now considered as separate entities. For example, before 2001, some of the cases of "renal cell carcinoma with sarcomatous differentiation" were proven to be "mucinous tubular spindle cell tumors" and are now reported as such.

4.2. Effects Of Medical Or Interventional Treatments Applied To The Removed Organ

Neo-adjuvant therapy is the treatment applied to the patient before surgery. Effects such as fibrosis, hyalinization and necrosis can be observed. Sometimes the tumor disappears completely in cases diagnosed by biopsy and receiving neo-adjuvant therapy. Each new treatment brings with it new effects and new possibilities of appearance in tissues. Fibrosis, hyalinization, secondary malignancy development, etc. in cases that received chemotherapy or radiotherapy. conditions can be seen. For example, neoadjuvant therapy is used quite frequently in breast cancer patients. After the treatment, resection is

performed and the presence of residual tumor is investigated. The oncological approach is shaped according to the residual tumor rate. The pathological examination of the specimens of patients who received neoadjuvant therapy is longer and more elaborate, both macroscopically and microscopically, than in ordinary patients.

4.3. Communication Expectations From Pathologists

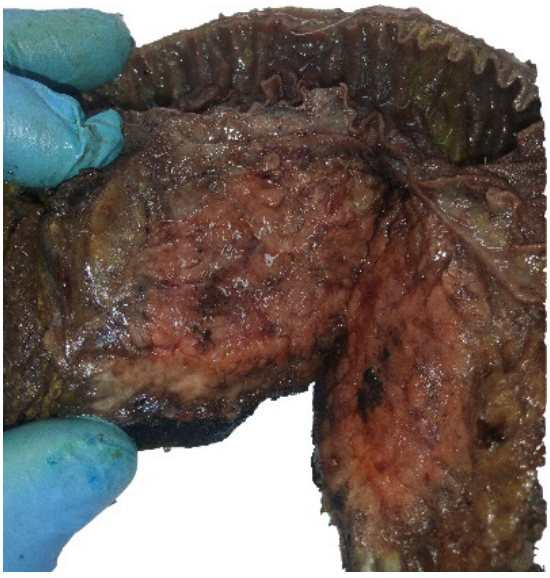
Pathologists are expected to be able to effectively communicate their findings to other healthcare providers. This includes providing clear, concise, and accurate information about the diagnosis and any recommended treatments. Pathologists should also be able to explain their findings to patients and their families in an understandable way. Additionally, they should be able to work with other healthcare providers to ensure that the correct course of treatment is taken.

4.4. Shortening Reporting Times

Expecting shorter reporting times from pathologists is reasonable, as technological advancements have enabled faster and more accurate diagnoses. Additionally, pathologists are expected to be able to work quickly and efficiently to provide timely results. Pathologists should also be able to communicate their findings quickly and accurately to other healthcare providers and patients. However, this expectation and the request to report faster than necessary can cause diagnostic problems. For example, in diagnoses that require immunohistochemistry/histochemistry/ direct immunofluorescence or molecular pathological methods, reporting before the process is completed may lead to misdirection in terms of the patient's treatment.

5. What To Do Before Large Specimens Reach The Pathology Laboratory Due To Surgeries That Can Be Performed Under Emergency Conditions

Formaldehyde is vital for a proper pathological examination. The appropriate volume of formaldehyde for the material to be taken in the operating room must be readily available. Formaldehyde should be used up to 10 times the volume of the specimen.



Picture 3. Whipple specimen opened for fixation

Specimens are sometimes left in the operating room in surgeries performed at the end of the day or on the days before holidays. In this case, formaldehyde cannot sufficiently penetrate large specimens and tissues lose their antigenicity. This situation affects the appearance of the tissue in routine staining and immunohistochemical staining. As early as possible, specimens should be opened appropriately and formaldehyde should be allowed to penetrate all of the tissue (Picture 3 and Picture 4). Formaldehyde fixation in normal tissues takes approximately 24 hours. In tissues containing bone, decalcification may be required after fixation. Acid-containing liquids are used for this. The decalcification process should be followed at intervals to avoid acid damage to the tissue. After the fixation is completed, other processes are started for embedding in paraffin. This process will pave the way for pathological examination to be performed by immunohistochemical and molecular methods.

Picture 4. Histerectomy specimen opened for fixation

6. Innovations Brought By Electronic Patient Files

The benefits of making patient files electronic include improving the accuracy and speed of medical records, reducing paperwork, and providing easier access to patient information. Electronic records are also more secure than paper records, as they are less vulnerable to errors and tampering. Additionally, electronic records can be shared easily between different healthcare providers, allowing for better coordination of care.

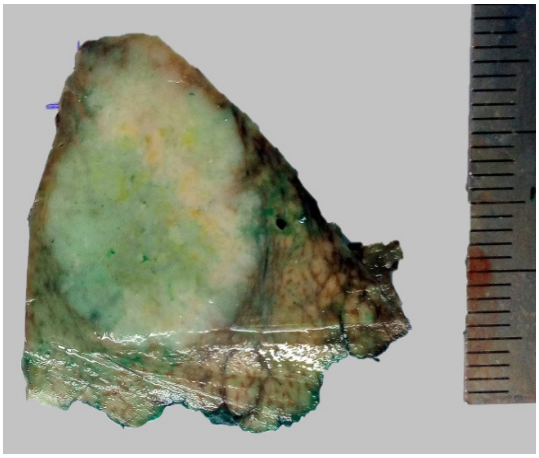
Thus, it is accepted that we know all the clinical and laboratory information of the patient. The fact that the information previously obtained through individual communication can be obtained over the computer has accelerated the reporting of the case and increased its accuracy. In addition to epidemiological data, there is a great acceleration and facilitation in scientific research with the digitization of pathological, radiological and oncological data.

7. Multidisciplinary Approach Can Be Achieved More Easily

The development of technology has made many examinations and imaging possible. For the most accurate management of the patient, a need for communication arose between the physicians who evaluated these examinations and imaging. Radiology, pathology, nuclear medicine, medical oncology and endocrinology have taken their places among the indispensable parts of the council meetings.

8. New Pathological Sampling Methods That Come With New Surgical Techniques

The macroscopic examination of specimens is a process in which the pathologist visually examines the specimen to identify any gross anatomical features. This includes examining the external features of the specimen, as well as any visible changes to the internal structure. This examination can be used to detect any abnormalities that may be present, such as tumors or other signs of disease.



Picture 5. A cross-section of the metastasectomy specimen performed for the tumor in the liver

When a new surgical method is developed, the surgical margins, distances between anatomical structures, etc., which should be considered in the specimen, should be redefined and maximum attention should be paid to sampling in accordance with the standard (Picture 5). For example, the evaluation of the tissue coming with the anvil material used for end-to-end anastomosis in colon resections was a procedure that was not performed before this device was used. It is very important to evaluate the tissue on this device as a surgical margin in correlation with surgeons.

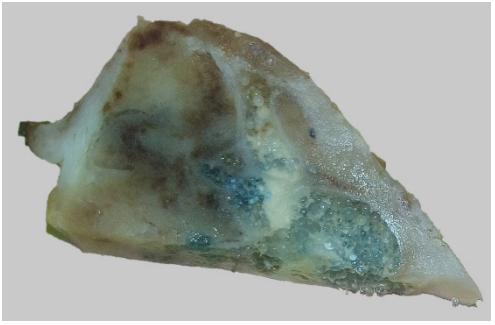
9. Reporting Recently Defined Prognostic Parameters

It is very important to determine the newly defined prognostic parameters and report the data obtained from the specimen. Necessary samples for macroscopic examination and molecular examination should be made and reported appropriately. The follow-up of the literature is of vital importance

in terms of specifying prognostic parameters. Examples include "tumor budding" and microsatellite instability tests, which, although not previously used in colorectal carcinomas, are now a routine part of reporting. For example, evaluation of RAS, BRAF gene mutations, microsatellite instability evaluation and PDL-1 evaluation in colorectal carcinomas are now among the routine evaluations. It should be implemented wherever possible. In histological examination, lymphovascular invasion, perineural invasion, condition of surgical margins, growth pattern and tumor budding are factors with prognostic importance. Some of these factors were not reported because their prognostic importance had not been proven before.

10. New Entities That Come With New Surgical Techniques

Newly developed surgical techniques have allowed us to see changes in tissues that could not be technically observed before. For example, transplanted organ biopsies, graft-containing resections, embolized tissues, ablated tissues are some of them (Picture 6). In some techniques, tissue properties show changes that we have not seen before after application. For example, we have limited data on fine needle aspiration cytology or the histopathological image that we will encounter in resection specimens, which are performed after ablation at a rate of atrane, since we have not undergone ablation therapy in the thyroid before. Therefore, after the development of the surgical method, some time and number of cases are required for the standardization of pathological evaluations.



Picture 6. It is seen that embolization is applied to liver tumor before resection

11. Direct Effects of Technological Developments on Pathology Routine

The direct effects of technological developments on pathology routine have been far-reaching. Automation and digital solutions are making it easier

for pathologists to access and analyze patient data quickly and accurately. Advanced imaging technologies such as digital microscopy, computer-assisted diagnostics, and telepathology are enabling more precise and detailed diagnoses. Additionally, artificial intelligence is being employed to facilitate more efficient and accurate diagnoses, while automated report-writing technologies are significantly reducing the amount of manual paperwork.

11.1. Automated Report Writing

Automated report writing in pathology is a growing trend that is revolutionizing the way pathologists work. Automated report writing software can streamline the process of writing pathology reports, allowing pathologists to easily create detailed and accurate reports. Automated report writing software can drastically reduce the amount of time spent on paperwork and free up time for more meaningful patient-focused activities. Automated report writing software can also reduce errors and inconsistencies associated with manual report writing.

11.2. Development Of Imaging Methods

The development of radiology and nuclear medicine methods has greatly benefited pathology. By combining imaging technologies with pathology, pathologists are able to make more accurate diagnoses and provide more comprehensive treatments. Radiology and nuclear medicine methods are also useful for identifying and tracking the progression of diseases, which can provide valuable insight into the cause of a patient's condition. Additionally, these methods can be used to detect and monitor cancerous cells and tumors.

11.3. Digitalization Of Slides

Digitalizing pathology slides, provides benefits in the following areas:

- Effect to reporting times: It will take some time to scanning whole slide. That cause a minimal increase in reporting time.

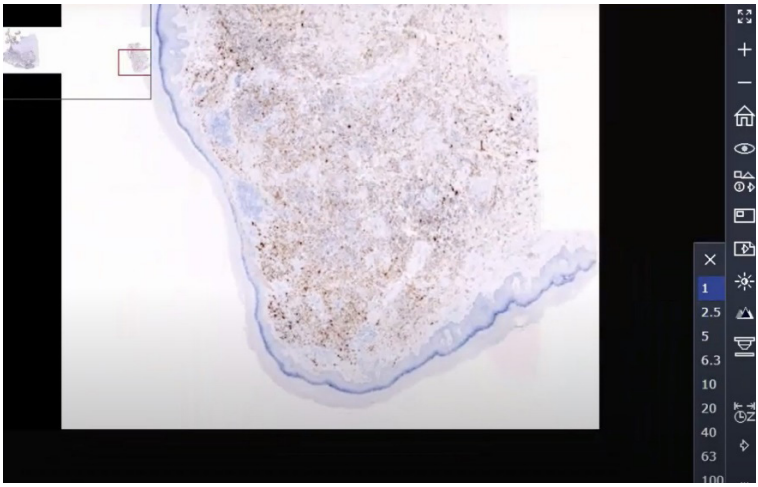
- Telepathology consultation: This will be the most useful way of digitalization. Adter scanning a slide, you can get in touch with any pathologists all around the world. It will save time and money at the same time.

- Using AI tools: Recently, AI tools have been developed for Ki67 proliferation index, HER2 scoring, and PDL1 assessment and are used in some centers. They are useful methods with proven effectiveness that can be used to save time in laboratories with a high number of patients.

- Taking shoots for researchs or articles: When we take photos from a microscope we need camera and software. But after digitalization that process will be already made by scanning device.

- It takes whole archive to your screen: In pathology routine, pathologists often want to look at old biopsies of patient, and that process take time and need human force. After digitalization of archive, it will take no time (Picture 7).

- Medical school education: Pathologists teach diseases to medical school students with their macroscopy and microscopy. The macroscopy portion can be demonstrated with brief laboratory visits and photographs. However, the microscopy part is a training that requires a longer time. Therefore, either only photographs will be contented with, or sufficient education will be provided by providing microscopes to all students. The digitalization of the laboratory eliminates all this need. Students can access the digital slides at any time through a website.



Pictıre 7. Digital pathology work station

11.4. Tissue Processing Automatization

Tissue processing automatization is the use of automated machines to process tissue specimens for microscopic analysis. Automated tissue processing machines can save time and increase accuracy by quickly and accurately processing tissue samples. Automation also eliminates the need for manual tissue processing, which can be time-consuming and labor-intensive. Automated tissue processing machines also allow for more consistent and controlled processing, reducing the potential for errors.

11.5. Staining Automatization

The automatization of staining in pathology is an important development that is making it easier for pathologists to prepare tissue samples for microscopic analysis. Automated staining machines can significantly reduce the amount of time spent on staining, allowing for more efficient and accurate diagnoses. Automated staining machines also reduce the risk of contamination and improve consistency when compared to manual staining. Automated staining machines can also be used to produce more detailed and accurate results.

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CHAPTER IV

INNOVATIVE APPROACHES TO THE PREVENTION OF PERIOPERATIVE HYPOTHERMIA: ACTIVE WARMING METHODS

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1. Regulation of Body Temperature (Thermoregulation)

The temperature of an individual is one of the five vital signs of a healthy individual. In a healthy human body, the temperature is maintained in the range of 36.0-37.5 through the effects of hormones, metabolism, and physical activity. The process of maintaining a body's temperature within normal limits is known as thermoregulation. Through thermoregulation mechanisms, an attempt is made to create a balance between heat input to the body and heat loss of the body. The thermoregulatory system consists of an afferent sensory organ, a processing center, and an efferent response organ. The processing center that controls the thermoregulatory set point in humans is the hypothalamus. Both heat-sensitive and cold-sensitive thermoreceptors are located in the afferent organ. Stimulation of cold-sensitive receptors activates efferent responses transmitted through the hypothalamus, reducing heat loss and increasing heat production. These responses include reducing blood flow to the peripheries and increasing heat production by mechanisms that include shivering. The heat center is stimulated by some factors such as infection, injury, inflammation, and antigenic changes.

In the case of hypothermia where the body temperature is below the normal limits in the human body, in the case of hyperthermia where the body temperature is above the normal limits, thermoreceptors are activated and some

changes are experienced. Physiological and behavioral changes that occur due to the activation of thermoreceptors are presented in Table 1.

Table 1. Physiological and behavioral responses to the activation of thermoreceptors

Body temperature stimulus	Increase	Decrease
Sensors	Peripheral and central thermoreceptors	Peripheral and central thermoreceptors
Control center	Hypothalamus	Hypothalamus
Effectors	1. Skin blood vessels 2. Sweat glands 3. Endocrine tissue 4. Behavior	1. Skin blood vessels 2. Arrector pili muscles 3. Skeletal muscles 4. Endocrine tissue 5. Behavior 6. Brown adipose tissue
Responses	1.Arteriolar and arteriovenous anastomosis vasodilation 2. Sweating 3. Decreased metabolic rate (adrenal and thyroid glands) 4. Reduced activity, stretched body position, and loss of appetite	1.Arteriolar and arteriovenous anastomosis vasoconstriction 2. Piloerection and air trapping 3. Shivering thermogenesis 4. Increased metabolic rate (adrenal and thyroid glands and brown adipose tissue) 5. Increased activity, huddled body position, andincreased appetite 6. Nonshivering thermogenesis

(Tansey & Johnson, 2015).

Even abnormal core temperature deviations of a few degrees will overwhelm the body's thermoregulation mechanisms, and temperature fluctuations outside the normal range can be fatal. For example, beyond body temperature of 42°C, cytotoxicity occurs with protein denaturation and impaired DNA synthesis, resulting in end-organ failure and neuronal deterioration. If body temperature falls below 27°C (severe hypothermia), the associated neuromuscular, cardiovascular, hematological, and respiratory changes can be equally fatal.

Factors determining the heat balance in the human body; can be grouped under three main headings as physiological heat balance mechanisms of the body, personal factors and environmental factors. Hormones can be given as an example to the physiological heat balance mechanisms of the body. Examples of personal factors are body surface area, dressing, and activity level. Examples of environmental factors are air temperature, humidity, air flow velocity and air quality. Body temperature is formed as a result of the metabolism of the food taken and the work of the muscles. Depending on the increase in the metabolic rate, heat production increases; As the metabolic rate decreases, heat production decreases. The most important factors affecting heat production in the body are:

Age: The body temperature of the elderly and children is lower than that of adults. With aging, shivering and vasoconstriction responses are delayed. With aging, thermoregulation slows as the functions of the hypothalamus, somatic and autonomic nervous systems slow down. Due to the decrease in muscle mass, the rate of heat generation of the body decreases. As the gastrointestinal system functions slow down, the absorption of nutrients to be used in heat production slows down. As the brown fat mass in the body decreases, heat production slows down and heat loss increases as thermal insulation decreases due to thinning of the subcutaneous fat tissue. The vascular response to temperature changes is delayed because the vasomotor reflex response is slowed. Vasoconstriction threshold decreases between 60-80 years of age. For this reason, along with the increased susceptibility to hypothermia, hyperthermia is also common as a result of the deterioration of the sweating mechanism. Although anesthesia disrupts thermoregulation in all age groups, its effect is more pronounced in elderly patients. Diabetes mellitus, heart failure, hypothyroidism, and cerebrovascular events that occur more frequently with aging affect heat production, distribution and expenditure. In newborns, the heat center is not fully developed. Therefore, the body temperature cannot be regulated well. Hypothermia (decreased body temperature) is seen in cold environment and hyperthermia (increase in body temperature) is seen in hot environment.

Gender: Due to hormonal factors, women's body temperature is more variable than men's. While the body temperature is normal until the ovulation period in the menstrual cycle, the body temperature rises with ovulation. During the menstrual period, the temperature drops again.

Physical activity: During physical activities, as a result of the work of the muscles, the metabolic rate increases and the body temperature increases.

Muscle work also increases tremor. If the body temperature drops too low, it is regulated by shivering.

Circadian rhythm: In daily life, there are main rhythms (cycles) that our body is under the influence of. The circadian rhythm is one of the cycles that most affect a person's life. The circadian rhythm covers the routines in our daily life cycle. The repetition of biochemical, physiological and behavioral rhythms within a 24-hour period is expressed by the term circadian rhythm. Body temperature varies throughout the day; It is low in the morning, gradually rises during the day, and reaches its highest level towards evening. Nutrition, physical activity and therefore metabolism are effective in these changes during the day.

Emotional state: Exposure to stress elicits endocrine, autonomic, and behavioral responses that allow an organism to adapt to a changing environment. As a result of physical and emotional stress, the sympathetic nervous system is stimulated, epinephrine and norepinephrine secretion increases, metabolism accelerates and body temperature increases.

Environment: Whether the air is cold or hot in the environment that the individual is in affects the body temperature. In addition, air flow rate and air quality affect body temperature. In hospital environments, patient rooms, beds and medical equipment that come into contact with the patient, and the fluids given to the patient also affect body temperature.

Hormonal factors: As the secretion of thyroid hormone and growth hormone increases, body temperature increases. As an important non-reproductive activity, female reproductive hormones also exert effects on the autonomous regulation of body temperature. Estradiol and progesterone affect thermoregulation both centrally and peripherally, where estradiol tends to promote heat dissipation and progesterone tends to promote heat preservation and higher body temperatures. Changes in thermoregulation with hot flashes during the menstrual cycle and at menopause are mediated by hormonal effects on skin blood flow and neural control of sweating. The effect of estradiol is to promote vasodilation, which causes greater heat dissipation in the skin.

Drugs: Antipyretic drugs lower body temperature. Some anesthetic drugs also have hypothermia-producing effects. Even in the postoperative period; Until the anesthetic drugs are removed from the body, hypothermia continues due to their effects on the central nervous system. Both general and regional anesthesia suppress the afferent and efferent control of thermoregulation. Thus, the body's response to cold is suppressed.

Shivering: Shivering is the first symptom that is noticed when the body temperature starts to drop, as it is the body's reflex defense to warm itself against the cold. Metabolic heat production increases in adults with thermogenesis accompanied by shivering.

Non-shivering thermogenesis: With non-shivering thermogenesis, it increases metabolic heat production without mechanical work. In this way, heat production is doubled in infants, but only slightly in adults. Skeletal muscles and brown adipose tissue are major sources of non-shivering heat production in adults. In non-shivering thermogenesis, heat is produced by catabolizing brown adipose tissue for heat production, not for ATP synthesis.

From time to time, hypothermia situations may occur in which the human body loses heat for various reasons. Understanding the formation mechanism of hypothermia will be beneficial in terms of prevention and effective intervention of hypothermia.

2. Occurrence of Hypothermia

Hypothermia is defined as when the body's core temperature is below 36°C. In thermophysiology, the thoracic and abdominal viscera and the brain are often referred to as the body core. The temperatures of these organs are considered core body temperature. There are a wide variety of circumstances and underlying causes that can cause hypothermia to occur. Heat loss in the body occurs in four different ways: radiation, convection, conduction and evaporation. While there is "dry" heat loss by conduction, convection and radiation, there is "moist" heat loss by evaporation through the evaporation of water in the skin or respiratory tract.

Radiation: Heat transfer by radiation describes the transfer of heat from the surface of one object to the surface of another object without direct contact. All objects at a temperature above absolute zero emit heat (infrared radiation). All surfaces around the object absorb this radiated heat. In the operating environment, the patient emits heat to the environment. Heat loss is transferred from the body to the environment by infrared waves. As the temperature of the environment decreases, the heat lost through radiation also increases. Heat loss by radiation is the main cause of heat loss in most surgical patients.

Conduction: Conduction is the transfer of energy from the high-energy part of a substance to the lower-energy part it is in contact with. In heat loss by conduction, the body comes into contact with a colder surface than its own heat

and heat is lost by transferring the heat to the contacted surface. Heat losses experienced when the operating table is cold and surgical instruments are cold can be given as an example of conduction type heat loss.

Convection: In heat loss by convection, there is heat loss from the body due to air flow. Air exchange in the operating room environment is much more frequent than in hospital environments outside the operating room. Heat loss occurs when the air in contact with the skin moves away from the body due to the air flow and is replaced by cold air. It is the mechanism that loses the most heat after radiation. Surgical drapes act as thermal insulators to minimize convective heat loss.

Evaporation: It is the loss of heat through the evaporation of water. In the case of heat loss through evaporation, the water becomes gaseous and takes the heat required to evaporate from the body area it contacts, causing the body to lose heat. In this way, the amount of heat lost by the body varies according to factors such as air flow, humidity of the air, respiratory rate of the patient, and the openness of the body surface.

Body heat loss that occurs in these four ways can occur in different situations and processes. One of the situations in which hypothermia occurs is the perioperative process. Hypothermia in the perioperative period is called perioperative hypothermia.

3. Perioperative Hypothermia

Perioperative hypothermia is one of the most common and serious conditions encountered during surgical procedures due to the redistribution of heat from the center to the periphery, impaired thermoregulation caused by anesthetic agents, and exposure to a cold environment that occurs during surgery. An estimated 20% to 70% of surgical patients experience hypothermia during their perioperative period. During some surgical procedures (e.g., cardiovascular surgery) and pathological conditions (e.g., traumatic brain injury), controlled hypothermia is also used by clinicians to reduce the metabolic rate of the patient. It should be noted, however, that hypothermia, which is a normal part of the surgical process, can be controlled or it can develop undesirably or uncontrollably as a part of the operation. Undesirable perioperative hypothermia may be caused by a variety of factors, including anesthetic agents, patient factors, and operating room conditions. The induction of anesthetic agents results in some physiological changes in the body. Inhibition

of the hypothalamus, which is involved in temperature control, by anesthetic agents leads to delayed activation of thermoregulatory mechanisms, making patients vulnerable to the risk of hypothermia. Inhibition of the hypothalamus by anesthetic drugs causes the thermoregulation system regulation range, which is normally activated in temperature deviations of 0.2 °C, to increase up to 4 °C and to be activated late. Different anesthetic applications have different roles in the formation of hypothermia. Epidural and spinal anesthesia both lower the threshold for tremor and vasoconstriction trigger (above the block level). The redistribution of heat is limited to half of the body. The internal hypothermia that occurs initially is not as pronounced as in general anesthesia. Vasodilation due to sympathetic block in central blocks causes much faster temperature loss. In addition, the central blocks suppress heat production by shaking. Hypothermia that occurs in central blocks continues until the end of the block. The risk of hypothermia increases in general anesthesia applications applied with neuraxial blocks. The synergistic effect of these methods lowers the vasoconstriction threshold by 1°C lower than in general anaesthesia. Moreover, regarding the patient and the operating room environment, preoperative fasting, anesthetized patients in a cold operating room environment, immobility during surgery and exposed body tissues are examples of factors that lead to hypothermia. Cold gases, inhalation of heat losses from body cavities, and exposure of body tissues can also lead to hypothermia. The onset of hypothermia following the induction of general anesthesia occurs in three stages. These stages are presented in the table below:

Table 2. Stages of hypothermia after anesthesia

Phase I (Redistributation phase)	It covers the first one hour period of the surgery. As a result of the redistribution of body heat from the center to the periphery (thermal redistributation), body temperature drops rapidly. The largest, sharpest drop in core body temperature is experienced.
Phase II (Linear phase)	It covers the 2nd to 3rd hour of the surgery. The core temperature decreases at a linear, gradual, slower rate. Body temperature drops below 35°C.
Phase III (Plateau phase)	It covers the 3rd to 5th hours of anesthesia. Peripheral vasoconstriction occurs during this period. Heat loss equals heat production. Thermoregulation is restored.

(Table 2 has been prepared by the author using the TSAR and Çimke et al. source specified in the references section.)

According to organizations such as the American Society of Anesthesiologists (ASA) and the National Institute of Health and Care Excellence (NICE), all patients should be assessed for hypothermia risk before the operation, and their body temperature should be monitored during the postoperative period, particularly for certain groups (patients who will undergo surgery longer than 30 minutes, in patients who undergo controlled hypothermia). Hypothermia is most reliably monitored at the following sites: the pulmonary artery, the distal esophagus, the nasopharynx, skin/axillary, bladder and the tympanic membrane. It is also important to apply preheating, heating IV fluids and keeping the ambient temperature within the recommended limits.

4. Incidence of Perioperative Hypothermia

Studies in the literature have reported that the incidence of perioperative hypothermia varies between 20% and 70% of patients who undergo surgery. These rates may also vary depending on factors such as the anesthesia technique applied to the patient, duration of surgery (long operation time), age of the patient (e.g., geriatric cases), gender, duration of mechanical ventilation, amount of fluid administered, and surgical procedure. For example, one study found that hypothermia occurred in 52% of total joint arthroplasty patients receiving neuraxial anesthesia (i.e., spinal, epidural). Sari et al. found the rate of perioperative hypothermia to be 78.6% in patients (n=2015) who underwent surgery under general anesthesia. In a study by Aksu et al. with patients who underwent surgery with different anesthesia techniques (general anesthesia, neuraxial anesthesia, peripheral block) in a university hospital in Turkey, the incidence of perioperative hypothermia was found to be 45%, and it was emphasized that patients who had thoracic and open abdominal operations were hypothermic at a higher rate.

5. Patients At High Risk Of Developing Perioperative Hypothermia

Perioperative hypothermia is more likely to occur in some groups. Awareness of risky groups by health care professionals involved in all stages of the surgical process will prove useful in terms of postoperative follow-up and preventative measures. These risk groups can be listed as follows.

- ASA II and above patients
- Geriatric patients
- Newborns and premature babies

- Patients with a body mass index below 25
- Those with cardiovascular disease
- Patients with comorbidities (e.g., anemia, diabetes, hypothyroidism, kidney disease)
- Trauma patients
- Patients who will undergo long-term surgery
- Brain tumor
- Those with systolic blood pressure above 140 mmHg
- Female gender
- Burn patients
- Patients undergoing major open cavity or abdominal surgery
- Those with fasting and fluid deprivation before anesthesia administration.

6. Complications That May Occur Due To Perioperative Hypothermia

Perioperative hypothermia may increase the overall oxygen consumption of patients and cause some complications. Perioperative hypothermia may lead to a higher incidence of cardiac complications, surgical blood loss, allogeneic transfusions, and surgical site infections. Moreover, perioperative hypothermia may lead to a decreased metabolic rate, the prolonged effect of some anesthetics, impaired pharmacodynamics, coagulopathy, transfusion requirements, thermal discomfort, increased incidence of postoperative nausea and vomiting, shivering, prolonged recovery and prolonged hospitalization period.

7. Active Warming Methods for the Prevention of Perioperative Hypothermia

Due to the potential for serious complications associated with perioperative hypothermia and its high incidence, the use of active heating methods during surgical procedures is becoming increasingly common. In parallel with technological advancements, active heating techniques developed for use during surgical procedures are increasingly used due to their convenience, noninvasiveness, and favorable outcomes compared with passive techniques. There have even been results suggesting the use of multiple active heating techniques that combine more than one active heating technique. Active heating methods are discussed under the following headings.

7.1. Circulating Water Systems (CWS)

There are two common applications of CWS: circulating water mattresses (CWMs) and circulating water garments (CWGs). The CWM includes a pad connected to the circulation pump and an electric heating chamber that maintains the temperature using hot water circulation. The mechanism underlying CWG is similar to that of CWM, but CWG uses a water-circulating garment that allows different parts of the body to be covered. Due to the higher specific heat capacity and thermal conductivity of water, circulating water systems theoretically offer a more efficient medium for transferring heat compared to air. Nevertheless, in studies comparing two different heating methods, the use of forced air had better results, resulting in this theoretical advantage of CWS not being translated into a clinical advantage. It has been suggested that CWS may be more effective and safer if placed above rather than below the patients, considering that it virtually eliminates metabolic heat loss. Furthermore, it should be kept in mind that there are opinions that pressure may increase the tendency for pressure heat necrosis due to decreased perfusion if placed under the patient.

7.2. Forced-air Systems

Forced-air systems are the most commonly used active heating technique to prevent hypothermia in surgical patients. Forced-air systems work on the principle of preventing heat loss through radiation and conduction. Hot air is generated by a motor and delivered to the compressed air blanket via a hose, thereby increasing peripheral tissue temperature and reducing central heat loss and blood cooling rate. These drapes have thin holes at the bottom that allow air to escape from the drape and envelop the patient. In the preoperative period, they can increase body temperature by approximately 0.75°C per hour. While forced-air heating systems are most commonly used with whole-body blankets for preoperative warming and postoperative rewarming, upper-body blankets are often preferred during surgery. Despite its easy and appropriate use in neonates, children, and patients with morbid obesity, it should not be used in patients who have had extensive burns. There have also been recent criticisms of forced-air systems as a potential source of surgical site contamination. However, there are also research results showing that forced air systems do not increase the risk of infection in the surgical incision site.

7.3. Resistive Heating (RH) Systems (Carbon, Gel, Electric Blankets)

RH systems are carbon fiber or polymer double-layer blankets with a circuit inside that converts electrical energy into heat energy, allowing heat transfer by conduction. A low-voltage electric current (15 V direct current) is utilized in carbon fiber-based models. The RH technique has several advantages, including its reusable nature, its ability to clean heating blankets, its affordability, its ability to heat a large portion of the body surface, its ease of operation during almost any type of operation, its quieter operation than forced air systems, and the ability to heat many independent parts of the body. Care should be taken to ensure that it is not wet during use, its temperature (to avoid burns) and that it is not bent during cleaning. Some resistive system covers may also contain water or a special gel. Water-containing covers pose a risk of burns. It is also recommended to be used with caution in obese, pediatric, and elderly patient groups. Depending on the type of surgery, different sizes of heating blankets may be preferred, such as chest and arm blankets. As these are systems that can come into contact with intact skin but not with mucous membranes, they do not pose a risk of transmitting pathogenic microorganisms to patients. Comparative studies have shown that RH systems are a highly effective and cost-effective method of heating compared to forced-air systems.

7.4. Radiant Warming Devices (RWD)

RWDs work on the principle of radiation and generate heat by converting the infrared radiation they emit into heat energy in the individual. The effectiveness of RWDs in warming the patient depends on the distance between the patient and the heater and the direction of the radiation. The safe distance for the use of RWDs is 80 cm. There are some pros and cons to using RWDs. The advantage of RWDs is that they do not come into direct contact with the patient's skin. The disadvantage is that since the working mechanism of the device is radiation, they cannot prevent heat loss through convection, which accounts for the majority of body heat loss. The use of RWDs is mainly limited to trauma and pediatric patients.

7.5. IV Fluid, Blood, Blood Product Warmers

The method of heating patients by heating the fluids to be infused into their bodies (for example, intravenous fluids, irrigation solutions, blood, and blood products) should not be considered an effective heating method alone since the

temperature of the fluids cannot exceed that of the body. However, since giving fluids to patients without warming them up to body temperature will lower their body temperature (approximately 0.25°C decrease in body temperature when 1 liter of fluid or blood is transfused at room temperature), warming the fluids to be given to patients can be considered a preventive method. Heating cabinets are used in some healthcare facilities as a method of providing heated intravenous fluids. In the study by Hong-Xia et al., fluid infusion was performed at different temperatures (first group with heated fluid at body temperature, second group at room temperature) in two groups of patients who underwent abdominal surgery. According to the findings of the study, heated fluid infusions kept patients normothermic and prevented shivering after anesthesia. While active warming methods are employed to warm a patient, IV fluid, blood, and blood products can be used to support the active warming methods.

7.6. Heat and Moisture Exchanger (HME) Filters

During spontaneous breathing, inhaled gases are heated and humidified in the nose and pharynx. However, when natural airways are bypassed during endotracheal intubation, patients are given cold and dry gases that need to be heated and humidified. HME filters can be used to humidify the transmitted gases. HME filters function by retaining heat and humidity during expiration and presenting them to the incoming dry medical gases during subsequent inspiration. HME filters have a number of advantages, including portability, light weight, and low cost. Moreover, HME filters serve numerous functions, including regulating temperature and humidity in the respiratory tract, protecting patients from contamination of anesthetic equipment, and ensuring that the anesthetic breathing circuit remains clean during anesthesia. Additionally, HME filters can help reduce heat loss and prevent tracheal damage from dry gases. Nevertheless, since the rate of heat loss through respiration in humans is low, it should not be considered alone as a method of preventing hypothermia but rather as a complement to other methods.

7.7. Negative Pressure Warming (NPW)

In the NPW technique, the patient's extremities are covered with special equipment and heated to 44-46°C with a negative pressure of 30-40 mmHg. NPW equipment has a glove-like structure that covers the hand and forearm. The purpose of NPW systems is to provide warming by improving subcutaneous

perfusion through the pressure applied. Thus, attempts have been made to prevent hypothermia in patients by transferring heat from the periphery to the center. However, since anesthetic agents are well-known vasodilators, the utility of NPW systems for further dilating peripheral vessels in the intraoperative setting is questionable. According to Smith et al., NPW devices were ineffective in accelerating the rewarming of hypothermic surgery patients following general anesthesia. In contrast, in a study by Rein et al., hot water vibrating NPW (warm water applied to a patient's arm in a clear acrylic cylinder and vibrating negative pressure applied) was significantly superior to forced-air heating (Bair Huggerw) in preventing and reversing hypothermia following laparotomy. Considering that NPWs are new and developing systems and that conflicting results have been reported in the literature regarding their effectiveness, further research on the subject will be insightful.

Conclusion: The use of passive methods, which can be called conventional methods, and active methods or a combination of active methods, should be studied to determine which method is the most effective in the prevention of perioperative hypothermia. To prepare the patient for surgery, it is recommended that the patient be warmed up beforehand. In the case of general anesthesia, it will be beneficial to begin warming the patient at least 10 or even 20 minutes in advance. Particular attention should be given to monitoring the body temperature of patients undergoing surgical operations lasting more than 30 minutes and patients who are at risk of hypothermia during surgery. Rather than treating postoperative hypothermia, it would be beneficial to prevent perioperative hypothermia and warm patients appropriately.

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CHAPTER V

ARTIFICIAL INTELLIGENCE IN SURGERY

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Artificial intelligence can be described as the computational simulation of self-learning, reasoning and self-correction processes. Much more rapidly than human capability, exponential improvements in data storage, computer power, and data digitalization are changing the medical field. Through playing hundreds of games against itself, artificial intelligence has recently continued to advance, and occasionally outperforms humans in chess-style competitions. It is thought that making medical decisions based on artificial intelligence analyses can lower mortality and morbidity rates in addition to improving patient care and diagnosis.

Artificial intelligence (AI) has the potential to revolutionize the field of surgery by improving patient outcomes, increasing the efficiency of the healthcare system, and assisting with tasks such as data analysis and decision support. In this series of papers, we will explore the current state of AI in surgery, including its applications, benefits, challenges, and considerations.

We will begin by examining the various ways in which AI is being used in surgery, including image analysis, diagnosis, and treatment planning. We will also discuss the potential benefits of AI in surgery, such as the ability to identify subtle signs of disease and develop personalized treatment plans.

Next, we will consider the challenges and considerations involved in implementing AI in surgery, including issues related to accuracy, reliability, bias, and ethics. We will also explore the role of surgeons in implementing AI into their practice and the importance of training and education in this process.

Finally, we will examine the future of AI in surgery and consider the potential impact of these technologies on the field and on patient care. By understanding the current state and future potential of AI in surgery, we can better prepare for the integration of these technologies into clinical practice and ensure that they are used safely and effectively to improve patient outcomes.

1. The Computer as Diagnostician

Many AI-based research in the literature examine how AI is used for diagnosis in emergency scenarios and how it may be a beneficial tool for patient screening and classification, according to physicians. By performing visual analysis of numerous medical images, artificial intelligence has the potential to dramatically improve diagnostic accuracy and allow early diagnosis. In many fields today, including the detection of skin lesions, the diagnosis of diabetic retinopathy, imaging results in radiology, and the identification of neoplasms in pathology, it is employed for diagnostic and predictive analysis of visual data.

Artificial intelligence research has been done on acute appendicitis due to the complexity of the diagnosis process, the ambiguity of the clinical symptoms, and the lack of unambiguous diagnostic indicators. In a retrospective analysis of 590 pediatric patients who underwent surgery for acute appendicitis and had histopathologically positive or negative results, supervised learning system is used to examine clinical data including Crp, leukocytes, basophils, monocytes, platelets, eosinophils, and neutrophils, as well as appendix diameter from ultrasonography This research led them to the conclusion that 2/3 of the patients who been found negative for acute appendicitis may avoid needless surgery and anesthesia.

In addition to numerical predictions, artificial intelligence may be employed for visual recognition. Investigations in orthopedics have looked into the use of artificial intelligence in diagnosing injuries to the extremities and to the spinal column. Convolutional neural networks for machine learning were used in a research to examine 4851 instances of proximal femur fractures. Diagnostic accuracy, sensitivity, and specificity were determined to be 96.1%, 95.2, and 96.9% in trials that solely employed plain radiography. Compared to orthopedists as well as other clinicians with medical specialties apart from orthopedics, these rates were significantly higher.

Another serious and perhaps fatal condition in surgery is intestinal obstruction. In the setting of bowel obstructions, diagnosis might occasionally

be challenging.neural network detection has 91.4% sensitivity and 91.9% specifity of diagnosing the intestinal obstruction.

2. Developing Autonomous Robots

One of the most drastic developments in surgical technology is thought to be autonomous robots. First and first, trustworthy, correct, and robust data are necessary to create autonomous robots. From here, further structural elements that often rely on computer vision may be laid. The deep learning method known as computer vision is used to comprehend visual data and handle tasks including object data recognition, classification, and segmentation. Contrarily, convolutional neural networks are a subset of deep learning algorithms built to handle data with inherent spatial invariance. Algorithms for segmenting and detecting objects pinpoint certain areas of an image that correspond to objects. The 2D surgical scene, depth map reconstruction, surgical expertise, surgical assessment, and surgical simulation and planning are some of the technologies currently required to construct autonomous robots.

3. Implications for Surgeons

The first major use of artificial intelligence is anticipated to include computers improving human performance. Collaboration between clinicians and machines has already been shown to speed up and boost decision-making. Pathologists can identify cancer-positive lymph nodes in breast cancer from 3.4% to 0.5% more accurately by utilizing artificial intelligence. Additionally, the rate of lumpectomy has been decreased by 30% in patients who had a high-risk lesion discovered by needle biopsy but had a benign outcome following lumpectomy as a consequence of artificial intelligence's ability to recognize high-risk individuals for breast cancer.

In the future, demographic and patient data augmentation will likely be available to and used by surgeons at every stage of therapy. Automated preoperative data analysis can produce patient-specific risk ratings for surgical planning and useful prediction data for planning postoperative care. Monitoring recovery and identifying problems can be aided by the integration of preoperative, intraoperative, and postoperative data. Any surgical procedure that has the potential to provide patient-specific and patient-centered care can use these models. As a result, the rates of morbidity and mortality can be improved.

Through the gathering of surgical footage and electronic medical records from several surgeons worldwide, artificial intelligence may be utilized to foster information exchange. This database of procedures and approaches can then be assessed based on outcomes. During the pre- and post-operative phases of therapy, video databases can utilize computer vision to gather and integrate data, capture unusual instances or anatomical details. Such potent database-driven analyses have the potential to provide large and significant advances in the development and validation of evidence-based procedures, as well as improvements in treatment quality.

4. The Surgeon's Role

Big data analytics are predicted to save the US healthcare system between $300 and 450 billion dollars annually, which implies there is a strong financial incentive to embrace artificial intelligence-based health data. Instead than waiting for the technology to be helpful, surgeons may be in a unique position to drive these breakthroughs.

Artificial intelligence's predictions are constrained by a lack of data. To make sure that all patients are covered, surgeons should work to increase involvement in regional, global, or local clinical data registries. Surgeons should investigate working arrangements with data scientists to collect new types of clinical data and assist in developing relevant interpretations of that data, since they are crucial participants in the development and implementation of AI-based technologies for surgical treatments.

By merging their understanding of anatomy and physiology with comparatively more complicated processes like disease pathophysiology and postoperative problems, surgeons may enhance the work of data scientists. These connections are crucial for accurately modeling and forecasting clinical occurrences as well as for enhancing the interpretability of machine learning methods. Surgeons and engineers must develop transparent, comprehensible algorithms in order to make use of the predictions and suggestions of artificial intelligence. Surgeons will need to develop a patient communication framework in order to transmit data made available by AI because they are the ones that provide clinical information to the patients ultimately. Understanding artificial intelligence is essential for effectively conveying to patients the outcomes of complicated analyses, such as risk projections, prognosis, and therapy algorithms.

5. Surgical Decision-Making

Surgical data science (SDS) is the application of data analytics and machine learning techniques to the field of surgery. It involves the collection, analysis, and interpretation of large amounts of data related to surgical procedures, patient outcomes, and other aspects of the healthcare system.

The goal of surgical data science is to make surgical decision-making process more accurate and healthy, improve the efficiency and effectiveness of surgical procedures, as well as the overall quality of patient care. For example, surgical data science can be used to identify patterns and trends in patient data, such as risk factors for complications or predictors of successful outcomes. This information can be used to develop better treatment protocols and improve patient outcomes.

Surgical data science can also be used to optimize the use of resources in the healthcare system, such as by identifying ways to reduce the cost of procedures or reduce the length of hospital stays. There are several ways in which surgical data science can be used to optimize the use of resources in the healthcare system. Here are a few examples:

- **Reducing the cost of procedures:** Surgical data science can be used to analyze the cost of different procedures and identify ways to reduce costs while maintaining the same level of patient care. For example, data analytics can be used to identify the most cost-effective treatments and procedures, or to identify opportunities for waste reduction.
- **Reducing the length of hospital stays:** Surgical data science can be used to identify factors that contribute to longer hospital stays and develop strategies to reduce the length of stays. This can help to reduce the burden on the healthcare system and improve the efficiency of patient care.
- **Optimizing the use of medical devices:** Surgical data science can be used to analyze the usage patterns of medical devices and identify opportunities for more efficient use. For example, data analytics can be used to identify devices that are underutilized or overutilized, and to develop strategies to optimize their use.
- **Improving patient outcomes:** By analyzing patient data and identifying risk factors for complications, surgical data science can help to improve patient outcomes. This can be achieved by developing more effective treatment protocols or identifying ways to reduce the risk of complications.

SDS is an interdisciplinary field that involves the collaboration of surgeons, data scientists, and other healthcare professionals that makes surgical decision making easier and accurate.

5.1. Implementation of Decision-Making Systems

5.1.1. Automated Electronic Health Records

Electronic Health Record Systems (EHRs) are generating large amount of data every year, and this data is a key model for AI models that needs large data sets. Electronic health records (EHRs) can be a valuable tool in supporting decision-making progress in surgery. EHRs provide a comprehensive, up-to-date record of a patient's health history, including information on previous diagnoses, treatments, and test results. This information can be accessed by surgeons in real-time, allowing them to make more informed decisions about a patient's care.

EHRs can also support decision-making in surgery by providing alerts and reminders to surgeons, such as notifications about potential drug interactions or contraindications. They can also provide access to evidence-based guidelines and protocols, which can help surgeons to make decisions that are in line with best practices.

In addition, EHRs can support decision-making in surgery by providing tools for data analysis and visualization. For example, surgeons can use EHRs to track trends in patient outcomes or to identify patterns in data that may not be immediately apparent. This can help surgeons to identify potential problems or areas for improvement in their practice and make more informed decisions about how to address them.

5.1.2. Use of Mobile Devices

Mobile devices, such as smartphones and tablets, can be useful tools in supporting decision-making progress in surgery by providing access to a range of information and resources. For example, surgeons can use mobile devices to access electronic health records (EHRs) and other databases, which can provide them with up-to-date information on patients' health histories, medications, and test results. This can help surgeons to make more informed decisions about patient care.

Mobile devices can also be used to access clinical decision support systems, which provide evidence-based recommendations and guidelines for the

management of specific conditions. This can help surgeons to make decisions that are in line with best practices and improve patient outcomes.

In addition, mobile devices can be used to access a range of diagnostic and visualization tools, such as medical imaging software and 3D modeling applications. These tools can provide surgeons with additional information about patients' conditions and help them to visualize and plan procedures more effectively.

5.1.3. Human Intuition

The implementation of human intuition into decision-making systems in surgery can help to improve the accuracy and effectiveness of these systems. Human intuition refers to the ability to make decisions based on experience, expertise, and a deep understanding of a subject. In surgery, human intuition can be particularly valuable in situations where data is limited or uncertain, or where the stakes are high.

There are several ways in which human intuition can be implemented into decision-making systems in surgery. One approach is to use machine learning algorithms that are designed to mimic human intuition by learning from examples of expert decision-making. These algorithms can then be used to assist surgeons in making decisions by providing recommendations based on patterns and trends identified in the data.

Another approach is to incorporate human input directly into the decision-making process. For example, surgeons can be asked to provide their expert judgment on specific cases or to review and validate the decisions made by the system. This can help to ensure that the decisions made by the system are informed by the expertise and experience of the surgical team.

6. Machine Learning in Surgery

Machine learning is a subfield of artificial intelligence that involves the use of algorithms and statistical models to analyze data and make predictions or decisions. In the field of surgical data science, machine learning is used to analyze large amounts of data related to surgical procedures, patient outcomes, and other aspects of the healthcare system.

Machine learning can be classified into four categories based on the type of feedback used for learning: supervised, semi-supervised, unsupervised, and reinforcement. In supervised learning, the machine is provided with labeled data

and explicitly told what to look for. In semi-supervised learning, the machine is trained on partially labeled data. In unsupervised learning, the machine is not given any labels or explicit instructions and must recognize patterns in the data on its own. Finally, in reinforcement learning, the machine receives rewards or punishments based on its actions and adjusts its behavior accordingly.

Classical machine learning algorithms, such as linear regression and logistic regression, can be used to analyze data and make predictions or decisions based on a set of predetermined rules. For example, a linear regression model could be used to predict the likelihood of a surgical complication based on a set of risk factors.

Advanced machine learning algorithms, such as neural networks and decision trees, can be more effective at identifying complex patterns in data. For example, a neural network could be used to analyze imaging studies and identify patterns that may indicate the presence of certain conditions, such as cancer. Decision trees can be used to analyze patient data and make decisions based on a series of branching conditions, such as whether a patient is at high risk for a certain complication.

In the field of surgical data science (SDS), computer vision technology can also be used to analyze large amounts of data related to surgical procedures and patient outcomes. Computer vision is the ability of computers to interpret and understand visual data, such as images and video. Machine learning algorithms can be used to improve the accuracy and reliability of this image and video analysis by allowing computers to learn from large amounts of data.

7. Transforming Information Into Intelligence in Surgical Education

Information can be transformed into intelligence through the process of learning and experience. In the context of surgical education, trainees can acquire knowledge and skills through a combination of classroom instruction, simulations, and hands-on training. As they learn and practice, they can apply what they have learned to real-world situations and make informed decisions based on their knowledge and experience.

Artificial intelligence (AI) can also play a role in transforming information into intelligence in surgical education. For example, AI can be used to create virtual reality simulations that allow students to practice surgical procedures and receive feedback on their performance. Surgical education primarily depends on both visualization and coordination, and AI-driven virtual reality simulations

can interact with trainee's visual fields. Use of augmented reality that interacts with elements of virtual reality is named "mixed reality technology." There are various studies on various devices that enable the application of this technique and their use in surgery. In a meta-analysis on the use of "smart glasses" in the surgical setting, it was suggested that smart glasses provide convenience in remote communication, but the use is not yet feasible due to "technical problems".

8. Building an AI-competent Surgical Workforce

The use of artificial intelligence (AI) in surgery is growing rapidly, and it is becoming increasingly important for surgeons to be competent in its use. To ensure that surgeons are prepared to effectively incorporate AI into their practice, it will be necessary to implement a range of strategies and programs that provide them with the knowledge and skills they need to use these technologies safely and effectively.

One approach to building an AI-competent surgical workforce is to provide educational programs that teach surgeons about the use of AI in surgery. A review of the literature suggests that these programs could be offered as part of professional development initiatives or as part of formal surgical education programs. They could cover topics such as the principles of AI, the ethical and legal considerations of its use, and the practicalities of integrating it into surgical practice.

Another strategy is to facilitate collaboration between surgeons and AI experts, such as data scientists and engineers. These experts can provide valuable guidance and support in the development and implementation of AI solutions, helping surgeons to overcome technical challenges and understand the limitations of these technologies.

The use of AI-powered training tools, such as virtual reality simulators and machine learning algorithms, can also be a valuable way to help surgeons improve their competency in the use of AI. These tools can provide a safe and realistic environment in which surgeons can practice using AI and develop their skills. Finally, it will be important to establish clear guidelines and regulations for the use of AI in surgery. This could involve the development of best practices guidelines, the establishment of oversight committees, and the creation of certification programs for AI-competent surgeons. Such measures can help to ensure that AI is used safely and ethically, and that patients receive the highest quality care.

Overall, building an AI-competent surgical workforce will require a collaborative effort from surgeons, AI experts, and regulatory bodies. By investing in the education and training of surgeons and establishing clear guidelines for the use of AI, it will be possible to ensure that surgeons are well-prepared to effectively incorporate these technologies into their practice and deliver the highest quality care to their patients.

10. Pitfalls and Barriers of Artificial Intelligence in Surgery

There are a number of potential pitfalls and barriers to the use of artificial intelligence (AI) in surgery. Some of the main challenges and considerations include:

Accuracy and reliability: One key challenge in using AI in surgery is ensuring that the systems are accurate and reliable. This may involve extensive testing and validation to ensure that the systems are providing reliable and accurate results.

Bias: There is also a risk of bias in the algorithms and data used to train AI systems, which can lead to unfair or inaccurate results. Ensuring that the data used to train AI systems is representative and free from bias is essential to ensure that the systems are fair and unbiased.

Ethical considerations: The use of AI in surgery raises a number of ethical considerations, including issues related to patient autonomy, informed consent, and confidentiality. Ensuring that these issues are adequately addressed is crucial to the responsible and ethical use of AI in surgery.

Cost: Implementing AI systems in surgery may also be cost-prohibitive for some healthcare systems, particularly in resource-limited settings. Finding ways to make these technologies more affordable and accessible will be important to ensure that they are widely available and can be used to benefit patients.

Lack of understanding: There may also be a lack of understanding or acceptance of AI among some surgeons, which can be a barrier to adoption. Ensuring that surgeons are adequately trained and educated about the benefits and limitations of AI will be important to overcome this barrier.

In conclusion, the use of AI in surgery is growing rapidly, and it is becoming increasingly important for surgeons to be competent in its use. To ensure that surgeons are prepared to effectively incorporate AI into their practice, it will be necessary to implement a range of strategies and programs that provide them with the knowledge and skills they need. These strategies could include

educational programs, collaboration with AI experts, the use of AI-powered training tools, and the establishment of clear guidelines and regulations for the use of AI in surgery. By investing in the education and training of surgeons and establishing clear guidelines, it will be possible to ensure that surgeons are well-prepared to effectively incorporate AI into their practice and deliver the highest quality care to their patients.

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CHAPTER VI

ADVANCES IN BARIATRIC SURGERY

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Obesity is a global pandemic and is a leading cause of mortality and morbidity. According to WHO, obesity is defined as excess fat accumulation resulting in health issues. Obesity is classified according to body mass index. WHO classification of obesity is demonstrated in Table 1. Lifestyle changes, diet, exercise, and medical treatments sometimes are insufficient at combating obesity. As a result, interventional and surgical methods have been utilized to treat obesity. Surgical management of obesity goes back to the 1950s when ileocolic bypasses were performed. Of course, early surgical treatment came with many side effects such as diarrhea and electrolyte imbalances. In the 1970s, Roux-en-Y gastric bypass was used in order to treat obesity and it is utilized to this day. Laparoscopic procedures became popular in the 1990s and from thereon, the progression of bariatric surgery kept moving. Currently, laparoscopic sleeve gastrectomy and roux-en-y gastric bypass have become the most popular choices for patients. Since laparoscopic roux-en-y gastric bypass is a challenging surgery, a mini gastric bypass/ "omega loop" was developed in 1997. In addition to surgery, endoscopic procedures have been developed to treat obesity. Due to their less invasive nature, endoscopic procedures have gained popularity over the years. Additionally, bariatric surgery is indicated for patients in obesity classes III and class II with obesity-related comorbidities, however less invasive, endoscopic procedures can be utilized in class I patients also.

Table 1. WHO Classification of Obesity

BMI	Obesity Class
30-34.9	I
35-39.9	II
>40	III

1. Single Incision Laparoscopic Surgery (SILS)

The first uses of SILS were in the 1960s during a tubal ligation operation. In general surgery, SILS was first used during an appendectomy in 1992. SILS for bariatric surgery was utilized in 2008 for sleeve gastrectomy and adjustable gastric banding. Most of the surgeons either used the umbilicus or the left upper quadrant of the patient for the main trochar. In some cases, additional trocars were placed either due to hemorrhages, adhesions or retracting bulky livers. Decreased mobility due to use of one multi-port trocar was also a disadvantage and may require a learning curve. Gradually decreasing the number of trocars may help the surgeon to make the transition to SILS.

SILS may also be used for adjustable gastric banding and roux-y gastric bypass. Gastric banding is relatively a simpler procedure compared to sleeve gastrectomy and can easily be performed through SILS. Roux-y gastric bypass is a more complex procedure with two anastomoses; an umbilical port is recommended in order to reach both sites of the anastomoses more readily.

The cosmetic outcome of SILS is superior to conventional laparoscopic procedures, especially SILS performed through the umbilical incision. Since the incision for the multi-port trocar is larger, incisional hernia has been a worry for the surgeons. Incisonal hernia would cause inferior cosmetic results and also carry future risks for intestinal strangulation which can be a serious health matter. European Hernia Society recommends for incisions over 10 mm, fascia should be sutured carefully. *Barutcu et al.* found that obesity and previously existing umbilical hernia is a risk factor for incisional hernia development.

2. Gastric Aspiration

This is an endoscopic weight loss method using a gastrostomy tube to partially aspirate 30% of the digested food in the stomach. Total body weight loss was approximately 18% in the first year. A decrease of 1% in levels of HbA1c was also noted. Levels of triglycerides, fasting glucose levels, and blood pressure were also reduced. The aspiration tube (called the “A-tube”) placement

is very similar to the placement of a PEG tube. Majority of the patients did not require overnight stay at the hospital and sedation was enough. The aspiration process can be done by the patient, after the meals, and takes approximately 10 minutes. There were a few notable complications e.g. peritonitis in one patient, buried bumpers, and tube rotation. Out of the 47 patients, 4 of them had cases of persistent fistulas after removal of the tubes.

Overall, this method was considered a safe treatment for obesity. It was reported that patients in the study felt empowered and in control of their weight loss journey by actively participating in the process of aspiration and taking "aspiration holidays" and breaks when needed. Another advantage was that patients were able to tolerate larger meals on special occasions e.g. birthdays unlike the patients with reduced gastric volumes after treatments such as sleeve gastrectomy. In conclusion, gastric aspiration is an FDA approved device and can be a safe weight loss modality for patients in the obesity classes II and III.

3. Intragastric Balloon

Intragastric balloons are space-occupying devices placed endoscopically. Main weight loss mechanism is thought to be space-occupying and delayed gastric outlet. There are several types of intragastric balloons with different fillings (liquid or air), adjustability, duration (6 months vs 12 months). According to *Neto et al.* there is no significant difference in the weight loss rates between different types of balloons.

Since intragastric balloon placement is considered to be a minimally invasive and safe procedure, it has a wide variety of uses. Intragastric balloon placement can also be utilized in overweight patients who don't qualify for surgical weight loss methods or the morbidly obese who are not able to tolerate surgical treatments. Intragastric balloon placement can also be a bridge for obese patients before weight loss surgery (or any other type of surgery).

In the paper by *Neto et al.* a consensus was reached by Brazilian surgeons, compiling more than 40000 patients with intragastric balloon placement. These scientists worked to establish a guideline. In the guideline, minimum age of the patient was decided as 12 years old and minimum BMI as 25 kg/m2. There are absolute contraindications: ulcers (gastric, duodenal or esophageal), previous gastric surgery, gastric and esophageal varices, hiatal hernia >5 cm, and anticoagulant use.

There are several possible adverse effects that require explantation of the balloon. These side effects include: moderate to severe pancreatitis,

gastrointestinal bleeding, ulcers (especially with nonadjustable balloons), persistent antral impaction, and persistent electrolyte imbalances. Many of these side effects can be managed conservatively and overall the intragastric balloon is thought to have a safe profile.

In conclusion, intragastric balloon placement is a relatively safe and effective weight loss method which can be used as both the final treatment and as a bridge to bariatric surgery.

4. Transpyloric Shuttle

Transpyloric shuttle works by interfering with gastric emptying. It has two bulbs connected to each other: one stays in the antrum, the other in the duodenum. The bulb in the antrum is larger and helps the shuttle stay in place. One advantage is that the shuttle doesn't need to be anchored physically. The device intermittently blocks the gastric outlet and therefore increases satiety. In a study by *Sartoretto et al.* patients continued to lose weight after the device was removed in 6 month and 12 month follow ups.

The most common side effects were nausea, abdominal pain, and reflux. There have been cases where patients presented with gastric ulcers however there were no complications and ulcers were treated medically. In conclusion, although the device is effective in both reducing BMI and improving metabolic parameters, its safety profile is still not ideal. The device has been approved by the FDA for treatment of obesity.

5. Endoscopic Sleeve Gastroplasty (ESG)

In Endoscopic Sleeve Gastroplasty (ESG), endoluminal suturing is utilized in order to alter the stomach shape similar to the shape in sleeve gastrectomy. Patients who don't fulfill the BMI criterion for sleeve gastrectomy or who are afraid to have "real surgery" may prefer this method. Endoluminal suturing is utilized to reduce 70% of the gastric volume. One difference compared to regular laparoscopic sleeve gastrectomy is that the length of the stomach is also reduced by 30%.

Hedjoudje et al. found in their metaanalysis that ESG is a viable and safe method for weight loss. In a multicenter study by *Sartoretto et al.* patients were discharged the same day, compared to an average hospital stay of 3-4 days after sleeve gastrectomy. The total body weight loss at 6 month follow-up was approximately 15%.

Out of 112 patients, 2 patients had severe side effects i.e. gastrointestinal bleeding. One of the patients had predisposing factors (low molecular weight heparin and warfarin usage). Another complication was perigastric fluid collection however this was also managed conservatively.

Overall, ESG is a safe and effective method for weight loss with more than 60% of patients having more than 10% total body weight loss in the first 3 months.

6. Primary Obesity Surgery Endolumenal (POSE)

The technique is called Primary Obesity Surgery Endolumenal (POSE); it makes full-thickness plications in the fundus and body of the stomach. This method is achieved by using an incisionless operating platform system (IOP). Anchors placed in the gastric fundus reduces the gastric volume and tolerance of the fundus to the food. Anchors placed in the distal gastric body work to delay the gastric emptying.

Delayed gastric emptying is thought to be the main mechanism for weight loss therefore a novel approach was developed called the distal POSE. In distal POSE, anchors are only placed distally in the gastric body and the fundus is spared; using delayed gastric emptying as the main mechanism for weight loss.

One of the main advantages of the POSE procedure is that the gastric anatomy is not permanently altered and the procedure can be reversed if need be. According to *Singh et al.* POSE is an effective and safe method for weight loss and is superior to lifestyle interventions alone; however this method may still not be as effective as bariatric surgery, especially in the long run. POSE has comparable results to ESG and according to *Saumoy et al.* the learning curve of POSE is shorter than that of ESG.

7. Endoluminal Magnetic Partial Jejunal Diversion (EMPJD)

This is a new approach that places magnets in the proximal jejunum and distal ileum to create a side-to-side jejunoileal anastomosis with enteral diversion using the incisionless magnetic anastomosis system (IMAS). Magnets are placed using colonoscopy and enteroscopy however additional laparoscopy is also utilized in order to measure the distances of the magnets within the bowels and chaperone the magnets during coupling. The magnets leave the gastrointestinal tract by defecation in approximately two weeks. This method's main mechanism of action is through malabsorption. Partial jejunal diversion helps most of the

ingested meal to bypass the small bowel causing malabsorption and weight loss. Since the food enters the ileum early on, GLP-1 (glucagon-like peptide 1) and Peptide YY is secreted earlier, inducing satiety and better glucose metabolism. It was shown that HbA1c levels decreased to 5.9 from 7.8 in diabetic patients and postprandial glucose levels improved. The total body weight loss was 14.6% in the first 12 months.

This is a very new approach and the first human pilot study was conducted by *Machytka et al.* in 2013 with 10 patients. Patients were discharged from the hospital the following day and were informed to consume a liquid diet for 2 weeks. Follow-up endoscopies were performed at 2, 6, and 12 months to check on the anastomosis. No adverse effects e.g. fibrosis, scarring were reported; only one patient had to undergo endoscopy for retrieval of the magnets. All of the patients had diarrhea post-procedure. Diarrhea was managed by nutritional changes and loperamide use.

Overall, EMPJD seems to be an innovative and relatively safe approach for weight loss. Long term studies with more patients may help shed light on the future potential of this method.

8. Laparoscopic Adjustable Gastric Banding (LAGB)

Laparoscopic gastric banding is a procedure where a gastric band is placed 1-2 cm below the gastroesophageal junction. Although LAGB was first found in 1993, the procedure has gone through many modifications over the years. This method works by restricting calorie intake. LAGB lost its popularity in recent years due to variable weight loss results and complications such as gastric band erosion or migration. In a study conducted by *Nasri et al.* 75 patients, out of 435, required re-operation mostly due to erosion or slipping. Only one fifth of the reoperations were due to inadequate weight loss, the majority were due to adverse effects.

One of the advantages of LAGB is that conversion to sleeve gastrectomy or a roux-y gastric bypass can be performed easily. In conclusion, although LAGB is a relatively safe, FDA-approved treatment for obesity, it still has considerable side effects and is not as effective as sleeve gastrectomy.

9. Transoral Endoscopic Restrictive Implant System (TERIS)

This procedure works by endoscopically placing a prosthesis at the bottom of the cardia to reduce the volume of the stomach. Endoscopic gastric

plications must be made in order to attach the prosthetic device. In a trial by *Verlaan et al.* with 18 participants, 3 serious complications were encountered i.e. 2 pneumoperitoneum and 1 perforation (which happened during the gastric plication process). There have also been issues with the durability of the procedure; several of the patients experienced detachment of the anchors. Detachment of the anchors was mostly seen in the lesser curvature of the stomach and led to uninhibited passage of food. Although weight loss results were promising for the first 6 months, all of the devices had to be removed after the 6 month mark. After removal of the devices, keeping off the lost weight was challenging for some of the patients.

The procedure was thought to be an effective bridge to bariatric surgery by reducing the patient's weight and size of the liver. The first human trial was developed in 2008 and there have been limited long term studies to evaluate the safety and efficacy of this method. Since then, TERIS procedure has undergone several updates and developments; however in the end, it has been largely abandoned.

10. Duodenal-Jejunal Bypass Liner (DJBL)

The duodenal-jejunal bypass liner is a device that is placed endoscopically. This device mimics the effects of the roux-en-y gastric bypass by inhibiting the contact of food with duodenum and proximal jejunum. As a result, a decline is seen in both metabolic parameters such as HbA1c and total body weights of the patients. Total body weight loss was 14% at the time of the removal of the device. One of the advantages of this method is that the anatomy of the patient is not altered permanently. In a study conducted by *Betzel et al.* 20 out of 44 patients required early removal of the device (before completing 12 months). Three of the patients reported severe side effects: 2 of them developed hepatic abscesses and 1 of them had a device malfunction where a sleeve of the DJBL was detached from the anchor.

DJBL is one of the newer and more experimental methods and has not yet attained FDA approval. Although it is effective for the first 6 months of implantation, the procedure still has some drawbacks and long term safety profile is still being explored.

11. Intragastric Botulinum Toxin Injection

Botulinum neurotoxin is a polypeptide produced by *Clostridium botulinum* and has 7 different serotypes, from A to G. Botulinum toxin has a variety of uses

in medicine and is a strong inhibitor of muscular activity. Its mechanism of action is to block the release of acetylcholine. As the popularity of the endoscopic procedures for obesity increased, BTA (botulinum toxin) was considered as an option for obesity treatment. Although the key mechanism for weight loss is unclear, delayed gastric emptying and consequently increased satiety seems to be the key. Many studies focused on the antrum of the stomach in order to inhibit Cajal cells, the pacemaker cells of the stomach, and therefore delaying gastric emptying. Some of the studies have been focusing on fundus, working to inhibit the ghrelin secretion. Fundus also plays a key role in gastric accommodation; by reducing gastric accommodation, early satiety can be achieved.

According to a metaanalysis by *Chang et al.* BTA injection was not superior to saline injections in terms of total weight loss and BMI change. Patients with BTA injections had longer gastric emptying times and for patients with BMI >40 kg/m2 (class III obesity), the weight loss difference became significant.

Overall, BTA injection is a safe procedure for obesity treatment however its efficacy is still being explored. One of the advantages is that BTA injections can be used as a bridge to bariatric surgery.

Each of these procedures offers unique benefits and may be suitable for different groups of patients depending on their specific needs and circumstances. Despite these advances, bariatric surgery remains a complex and often challenging field, and ongoing research and development is needed to further improve outcomes and reduce the risks associated with these procedures.

It is important for patients to understand the potential risks and complications and to work closely with their healthcare team to ensure the best possible outcomes.

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CHAPTER VII

USAGE OF RADIOFREQUENCY ABLATION IN THYROID PATHOLOGIES

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1. Introduction

Thyroid nodules are very common in clinical practice, their prevalence is up to 50% depending on the way they are detected. Most of them are hyperplastic nodules, and clinically they are not malignancy-related neoplasms. However, it is malignant at a rate in the range of 7-15%, although not at high rates, and in less than 1% of cases it becomes clinically significant and even fatal for the individual. There has been a 2.4-fold increase in thyroid malignancies in the last 30 years. For most of these nodules, evaluations by clinical examination, neck ultrasound, thyroid function tests, and sometimes fine needle aspiration (FNAB) are sufficient to conclude that they can be safely observed in the long term. However, growing and benign nodules that cause local compression symptoms, toxic nodules and nodule malignancy with a marked asymmetry of the hosts for different nodules that cause aesthetic concerns sometimes on the neck there is a need for a management plan. The standard treatment in these cases is surgery, either total thyroidectomy or lobectomy, depending on the characteristics of the disease.

Radioactive iodine (RAI) is also a treatment option for toxic nodules. However, both options, especially surgery, often result in the removal of more of the affected thyroid parenchyma, leading to the development of hypothyroidism. Also, surgery has an undesirable effect on the neck, such as a scarring and risk of complications (dysphonia and/or hypoparathyroidism). In contrast, although RAI does not carry these risks, it may not be preferred in some patients due to its adverse effect on pregnancy, young children in close contact, and the potential risk of secondary malignancies. Therefore, the need for additional therapeutic

options is obvious. Although chemical ablation with percutaneous ethanol injection is less expensive and requires less costly equipment, it is considered the treatment of choice for cystic nodules and tends to be less effective for solid nodules. The therapeutic effect of radiofrequency ablation in cystic nodules is similar compared to ethanol ablation.

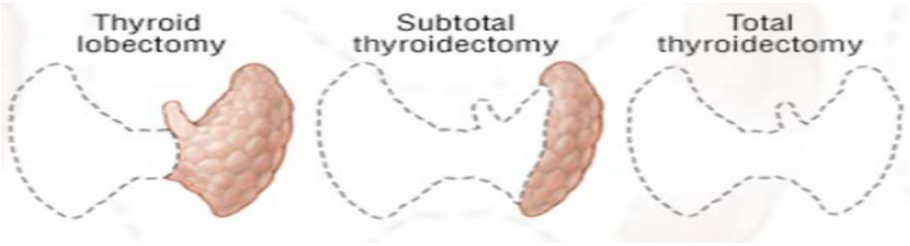

Figure-1: Types of thyroidectomy

Table-1: Comparison of Efficacy for Cystic Thyroid Nodules between EA and RFA (EA:Ethanol Ablation)

		EA				RFA			
Number	Authors	Sampl Size	Nodule Volume at Baseline (mL)	Nodule Volume after Treatment (mL)	VRR (%)	Sample Size	Nodule Volume at Baseline (mL)	Nodule Volume after Treatment (mL)	VRR (%)
1	Baek et al.	24	14.7	2.45	83.1	22	8.6	1.1	87.1
2	Sung et al.	36	13.83	0.95	93.1	21	10.19	0.79	92.2
3	Sung et al.	25	12.2	0.38	96.9	25	9.3	0.62	93.3

Other thermal ablation techniques, such as radiofrequency ablation (RFA), microwave ablation, laser ablation, and high-intensity focused ultrasound (HIFU) ablation have been recommended by guidelines as safe and effective treatments for benign thyroid nodules. Many studies have reported a significant reduction in the volume of the nodules with improvement in local symptoms or cosmetic problems.

The use of radiofrequency currents to induce heat in tissue has been known for over a century, since the time of D'Arsonval. The predominant

form of percutaneous radiofrequency ablation (RFA) was discovered in 1990 by Mc Gahan et al. It was introduced as a treatment option in patients not suitable for open surgery.

2. Clinical Use of RF Ablation

In RF ablation, current flows from the device to the tissue to a floor plate, usually in the back or chest.

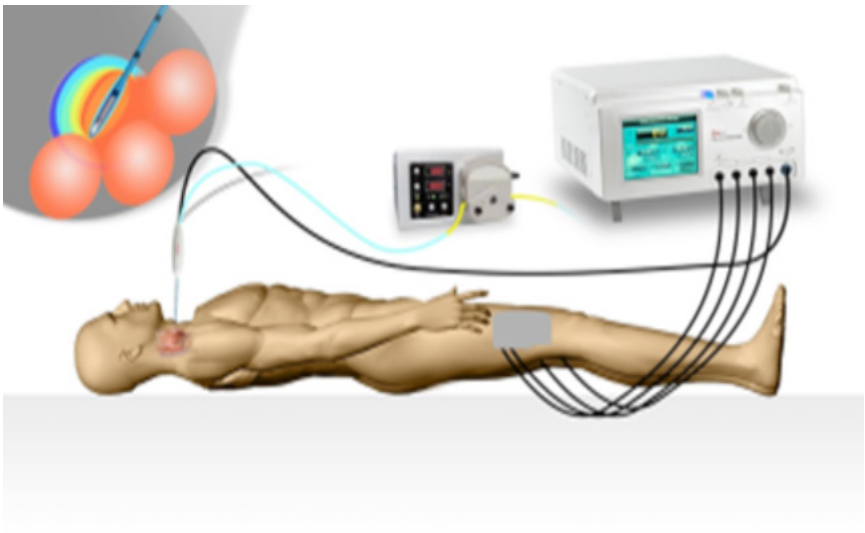

Figure-2: Monopolar radiofrequency circuit

The current causes ionic agitation in the tissue underlying the electrode of the device where the current density is highest, which generates heat in the tissue area around the electrode and is then conducted through the rest of the tissue. An increase in temperature causes irreversible changes such as protein denaturation, melting of the cellular lipid bilayer, and evaporation of the intracellular fluid leading to coagulation necrosis.

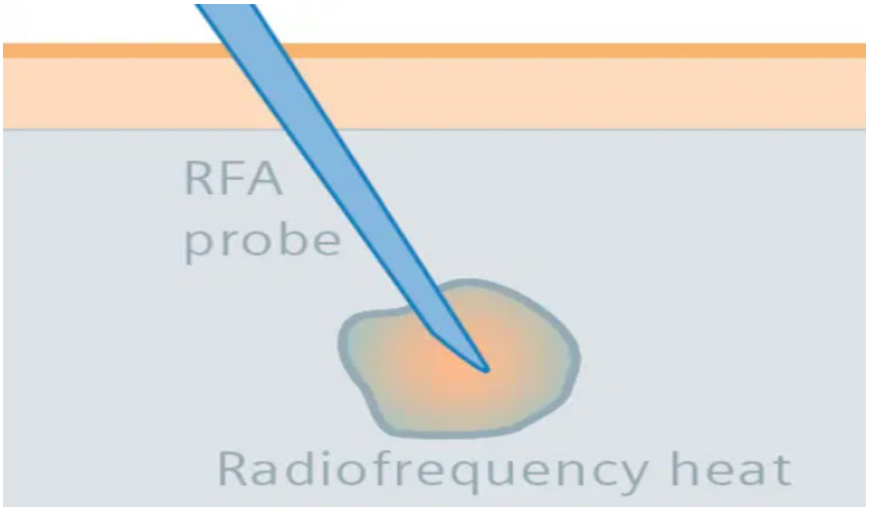

Figure-3: Radiofrequency heat

RFA has been recommended in certain centers since 2000 for the treatment of primary and metastatic liver, lung, bone and kidney tumors and for ablating abnormal conduction pathways in the heart. The last fifteen years have experienced rapid growth in the clinical use of RFA with high demand for minimally invasive treatment for a better quality of life.

3. Use of RF Ablation in Thyroid

Surgery is the most effective first treatment option in symptomatic benign thyroid nodules. However, outpatient alternatives that avoid surgery and preserve normal thyroid function have recently become available. Thermo-ablative methods induce local thermo-destruction, resulting in reduction of nodule size and improvement of local symptoms.

Monopolar radiofrequency ablation (RFA) is currently the best documented thermoablative method. Recent studies have demonstrated the efficacy and safety of thermal ablation in patients with low-risk papillary thyroid microcarcinoma (PTMC) and recurrent thyroid cancer where the risks of surgery outweigh the benefits, or in patients who refuse repeat surgery. There are European clinical practice guidelines and Korean consensus statement and recommendations guiding the appropriate use of radiofrequency ablation in thyroid nodules. In a systematic review of 17 retrospective studies, Monpeyssen et al. provided evidence for the efficacy of RFA in benign thyroid nodules in reducing nodular volume and compression and cosmetic symptoms without

causing thyroid dysfunction or life-threatening complications. Indeed, RFA is a percutaneous treatment that results in thermal tissue necrosis and ultimately fibrosis within the target nodule. As a result of this procedure, the nodules shrink with a 12-month volume reduction rate ranging from 67% to 75% for lesions with a single procedure. However, thermal ablation is an operator dependent technique and should be performed in centers with RFA-specific expertise. Meta-analyses found that RFA caused a significant reduction in tumor volume, maximum diameter, and serum Tg for locally recurrent thyroid cancers. Suh et al. A meta-analysis by RFA reported a complete response rate of 68.8% and a treatment-site recurrence rate of 0% after RFA. In addition, the serum Tg level reduction rate was 71.6%.

Table-2: Efficacy of RFA for Nonfunctioning Thyroid Nodules

Authors	Sample Size (Nodule Number)	Follow Up Period (Months)	Symptom Score at Baseline	Symptom Score after RFA	Cosmetic Score at Baseline	Cosmetic Score after RFA	Nodule Volume at Baseline (mL)	Nodule Volume after Treatment (mL)	VRR (%)
Ahn et al.	22 (22)	3.6	NA	NA	NA	NA	14.3	4.7	74.3
Aysan et al.	100 (100)	15.4	NA	NA	NA	NA	16.9	2.6	84.6
Baek et al.	15 (15)	6.43	3.33	1	3.6	1.53	7.5	1.3	82.7
Baek et al.	200 (200)	5.21	NA	NA	NA	NA	6.8	1.8	73.2

A long-term follow-up study (mean 48 months) of six patients with primary thyroid cancer reported that mean nodule diameter regression was 98% and four cancers had completely disappeared on USG.

Current guidelines from the American Thyroid Association indicate that two effective and relatively safe definitive treatment options for toxic AFTN are radioactive iodine (RAI) therapy and surgery. However, post-surgical hypothyroidism and RAI treatment may complicate pre-existing chronic diseases in the elderly and is controversial in younger women. Also, some patients refuse RAI treatment or surgery because of potential complications such as radiation exposure or hypothyroidism. As an alternative therapeutic modality, RFA in the treatment of AFTN has been reported in recent studies. An Italian group has suggested that AFTN-induced hyperthyroidism can be completely or at least partially treated with RFA when surgery and RAI are contraindicated or rejected.

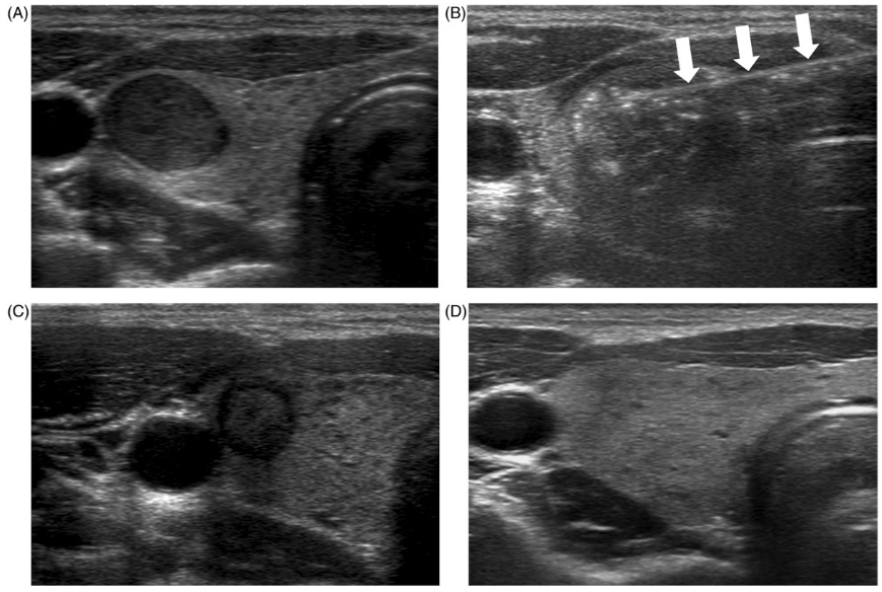

Figure-4: 31-year-old woman with a right thyroid nodule proven to be a follicular neoplasm on core needle biopsy. (A) A well-defined hypoechoic solid thyroidnodule on the transverse US image. (B) An echogenic totally ablated thyroid nodule with a RF electrode (arrows) on the transverse US image. (C) One month afterRFA, the nodule had decreased and there was no undertreated area. (D) Two years after RFA, the nodule had disappeared.

RFA therapy for follicular neoplasm is more controversial than PTC. Because in order to definitively diagnose whether the nodules are follicular adenoma compared to a carcinoma, surgical resection is necessary to exclude the presence of vascular or capsular invasion. However, a recent 5-year study involving 10 patients whose follicular neoplasm < 2 cm in size was detected as a result of a thyroid biopsy reported that RFA is safe and effective in the short term for such cases. it was shown that there was a significant decrease in the average volume of lesions, eight ablated lesions completely disappeared after a single treatment at the follow-up by Ha et al., and no recurrence was recorded (range: 60-76 months).

4. Technique

After local anesthesia and/or sedation, the RFA probe is inserted into the midline of the anterior neck at the level of the isthmus (called the trans-isthmic

approach) and the nodule is targeted using the "moving shot technique" in which the operator moves the RFA needle back and forth across the nodule while visualizing hyperechoic changes in tissue during ultrasound guidance.

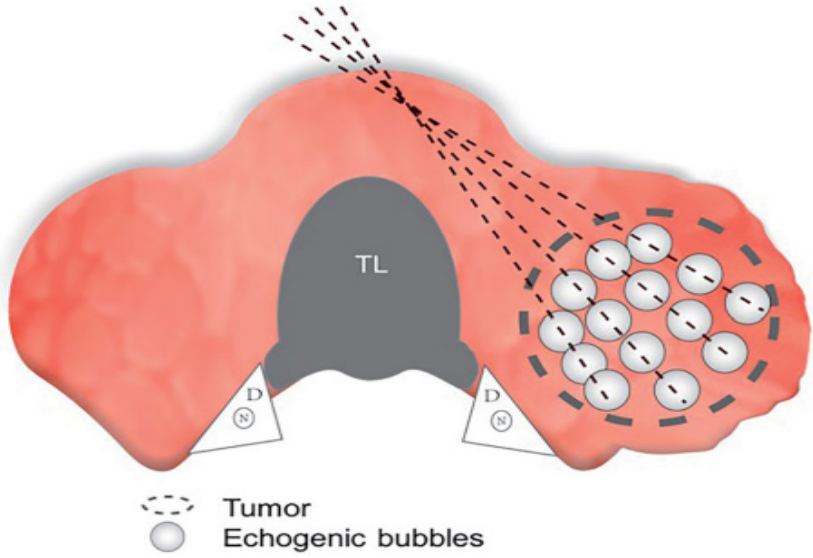

Figure-5: Moving shot technique

Heat from the electrode tip introduces a high-frequency alternating current that raises tissue temperatures from 60 to 100 degrees Celsius, causing tissue necrosis and fibrosis. Lidocaine injection can be used prior to ablation to anesthetic the thyroid capsule to hydrodissection, providing greater distance from the active RFA needle tip and vital surrounding structures, and also provides a heat sink around the nodule to prevent injury to these structures. A 5% dextrose solution (D5W) can be used to hydrodissect and create an aqueous barrier for areas that need to remain sensitive, such as the trachea, nerves, or other vital structures.

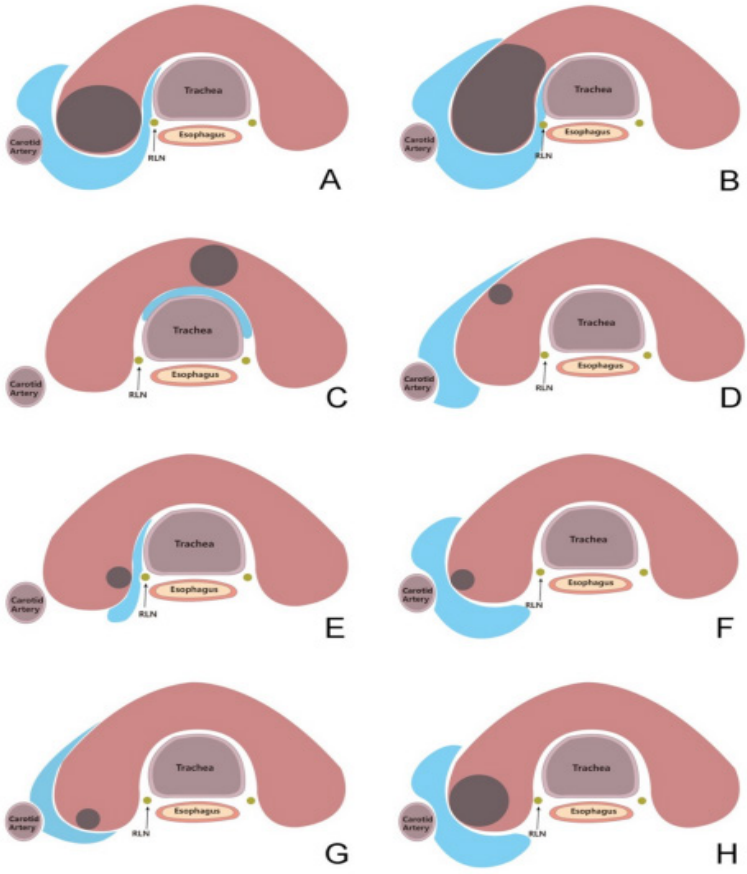

Figure-6: 2. "Hydrodissection technique" for nodules in risk areas. A-H, the range and effect of the hydrodissection for nodules in different location.

After tissue ablation, there are obvious sonographic features to guide the operator in real time. These include hyperechoic signals and 'microbubbling' as well as an increase in generator impedance as the tissue hardens, indicating coagulative necrosis. The operator approaches the tissue as "subunits" from the deepest to the most superficial part of the nodule. Operator should be careful to avoid extension of the probe beyond the posterior or lateral thyroid capsule, particularly within the "danger triangle" where the recurrent laryngeal nerve connects to the trachea near the posterior-medial aspect of the thyroid. Immediate shrinkage of the nodule is appreciated along with progressive shrinkage over months to years. In benign nodules, the volume of the nodule is typically expected to decrease by 50-90%, which may vary depending on both operator and tumor factors.

5. Complications

Radiofrequency ablation is safe and well tolerated and is associated with a low incidence of complications when performed by experienced operators. Although many studies have shown that thermal ablation is a safe technique, there are some associated complications that are mostly minor. In a meta-analysis of 12 studies by Cho et all, the overall complication rate was found to be 4.6% and the major complication rate was 1.3% in the RFA group treated with RFA, which included benign nodules and was followed for more than three years. In a systematic review of 2786 nodules (24 studies including both benign and recurrent thyroid cancers), the overall RFA complication rate was 2.38% and 1.35% for major complications. In the subgroup analysis, the overall and major complication rate was higher in recurrent malignant nodules (10.98%) than in benign nodules (2.11%).

Various complications have been reported including major complications such as nerve injuries (recurrent laryngeal nerve, cervical sympathetic ganglion, brachial plexus, and spinal accessory nerve), nodule rupture and permanent hypothyroidism, and minor complications such as hematoma, vomiting, skin burn, transient thyrotoxicosis, lidocaine toxicity, hypertension, and pain. However, no life-threatening complications were observed and the sequelae rate was 0.21%. Wang et al., in a systematic review in which they evaluated 3409 patients, found that the most common complications were sensation of heat and pain.

Bipolar RFA has some advantages compared with monopolar, such as no grounding pads are needed, so burns at the grounding pad site can be avoided. Bipolar RFA reduces the risk of RFA-related failure of implanted electrical devices, especially in elderly patients.

To reduce the risk of complications, the operator must closely monitor the lead tip during the procedure, should have a comprehensive knowledge of neck anatomy, and be experienced in image-guided interventions.

6. Result

RFA has an acceptable complication rate for the treatment of benign thyroid nodules and recurrent thyroid cancers and is a minimally invasive approach compared to surgery. In the future, the use of RFA for thyroid patologies will find widespread use with the increase of experienced operators.

Table-3: Complications following RFA of benign thyroid nodules from a systematic review of 3409 patients by Wang et al

Complications	N° cases
Pain and sensation of heat	281
Voice changes	32
Hematoma/hemorrhage	31
Vasovagal reactions	19
Nodule rupture	14
Horner syndrome	14
Increase in blood pressure	12
Nausea/vomiting	11
Fever	11
Cough	10
Skin burn	6
Recurrent nerve injury	4
Hypothyroidism	3
Needle track seeding	2
Thyroiditis and thyrotoxicosis	1
Brachial plexus injury	1
Pseudocystic transformation	1

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CHAPTER VIII

INNOVATIVE APPROACH IN THORACIC SURGERY: AWAKE VIDEO-ASSISTED THORACIC SURGERY

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1. Background

1.1. Definition And Terminology

VATS procedures, in which general anesthesia and tracheal intubation are not applied, have been variously named in the literature. The most commonly used of these nomenclatures are: Awake video-assisted thoracic surgery (AVATS), non-intubated thoracoscopic surgery, non-intubated video-assisted thoracoscopic surgery (NIVATS) and tubeless VATS.

Although there are publications on thoracoscopy applications performed under sedation in the 20th century, the term "awake thoracoscopic resection" in its current sense was used for the first time in the publication of Pompeo et al.

Throughout this book chapter, I will prefer to use the term "awake-VATS", with reference to its first use.

1.2. Brief History And Development Of Awake VATS

VATS applications differ from conventional methods in terms of requiring endoscopic surgical instruments, video camera system, high resolution monitor and special anesthesia management (Figure 1).

Lung isolation is of great importance in thoracic surgery operations, as it provides the surgeon with a suitable space for safe dissection and facilitates retraction of the lung. Double-lumen intubation, bronchial blocker, or advancement of a single-lumen tube to the main bronchus are the main methods used for lung isolation. However, general anesthesia and tracheal intubation

carry the risk of several complications. Especially mechanical complications that may be caused by intubation can cause high mortality and morbidity. In addition, many thoracic surgery procedures cannot be performed in patients who cannot tolerate lung isolation due to insufficient respiratory capacity.

The awake VATS method, which emerged from this point of view, has increased its popularity in the past 10 years with its successful results. Awake VATS approaches under local anesthesia were first published in the late 90s as minor surgical interventions. The first large case series was published in 2004 by Pompeo et al. In this report Pompeo et al. shared the results of 30 wedge resections performed with awake VATS, demonstrating the success and feasibility of the technique. Better patient satisfaction, less need for nurse care and shorter hospital stays have been shown among the advantages of the awake VATS method. The same method was also used in the treatment of spontaneous pneumothorax, with less cost and shorter hospital stays. When Vanni et al. compared VATS, procedures performed with local and general anesthesia, they found higher lymphocyte and natural killer cell counts on the postoperative 1st day in the local anesthesia group.

Awake VATS lobectomy for lung cancer was first reported by Chen et al. Operative complications were found to be 6%, and the rate of conversion to general anesthesia was 10%. Thus, it has been shown that major lung resections can be performed safely and successfully in a tubeless manner. As can be seen from the studies in the literature, awake VATS can be applied with many different indications, from minor interventions to major lung resections.

In this book chapter, it is planned to discuss the main features of awake-VATS including indications and contraindications, anesthesia techniques, and postoperative pain management.

2. Indications

Over time, with increasing experience, the indications for awake VATS have expanded from minor surgery to more complicated major interventions. Pleural/pericardial fluid drainage and biopsy, pleural interventions such as empyema deloculation and partial decortication, interventions for parenchyma pathologies such as bulla/bleb resection, wedge resection, lobectomy are within the indications.

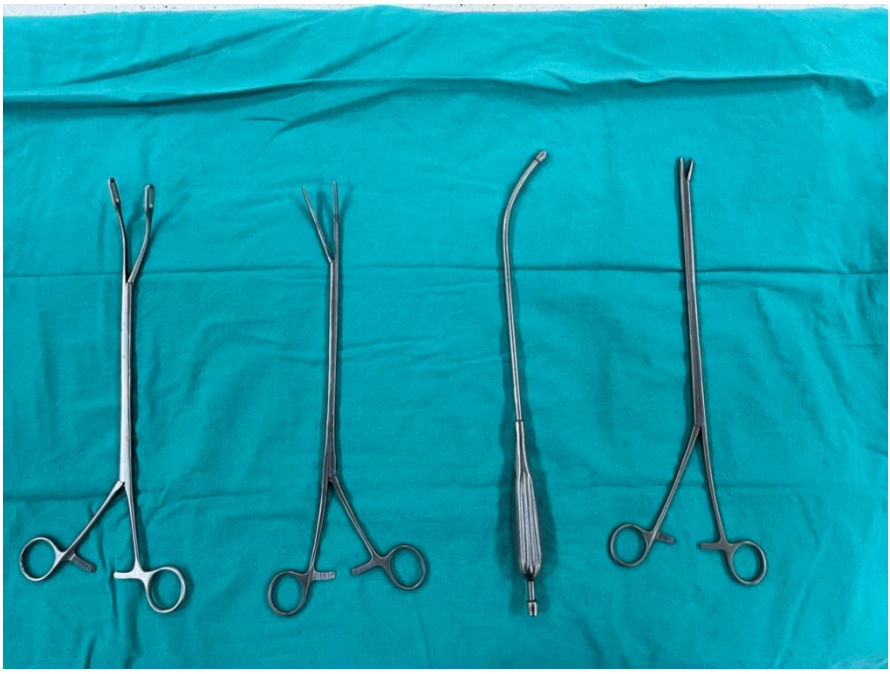

Figure 1. Endoscopic surgical instruments customized for video-assisted thoracic surgery.

However, it should not be forgotten that the variety of operations in which awake VATS can be performed is possible with a good preoperative preparation, the application of modern anesthesia methods and the successful application of minimally invasive methods.

2.1. Pleural Diseases

Awake VATS applications in pleural pathologies are frequently used for diagnosis purposes. The presence of pleural effusion or pleural nodularity that cannot be diagnosed clinically and radiologically is the most common indication. Biopsy from the pathological area under direct vision and simultaneous removal of loculations and allowing fluid drainage and sampling are important advantages. Exploration of the pleural cavity alone in this patient group provides important data on many issues such as pleural irregularity, diaphragm function and presence of loculation.

In the literature, awake VATS applications for pleural decortication in patients with empyema have also been reported. Although deloculation seems feasible, it is important to select the appropriate patient for the decortication

operation, which has a high risk of morbidity, even with thoracotomy in the intubated patient.

Small series in which the awake VATS method has been successfully applied in the surgical treatment of primary spontaneous pneumothorax, another common pleural pathology, have been published. It is stated as a feasible method because there is no need for dissection of the anatomical structure that poses a risk for bleeding, and only a few wedge resections (Figure 2) and pleural abrasions are sufficient in most cases.

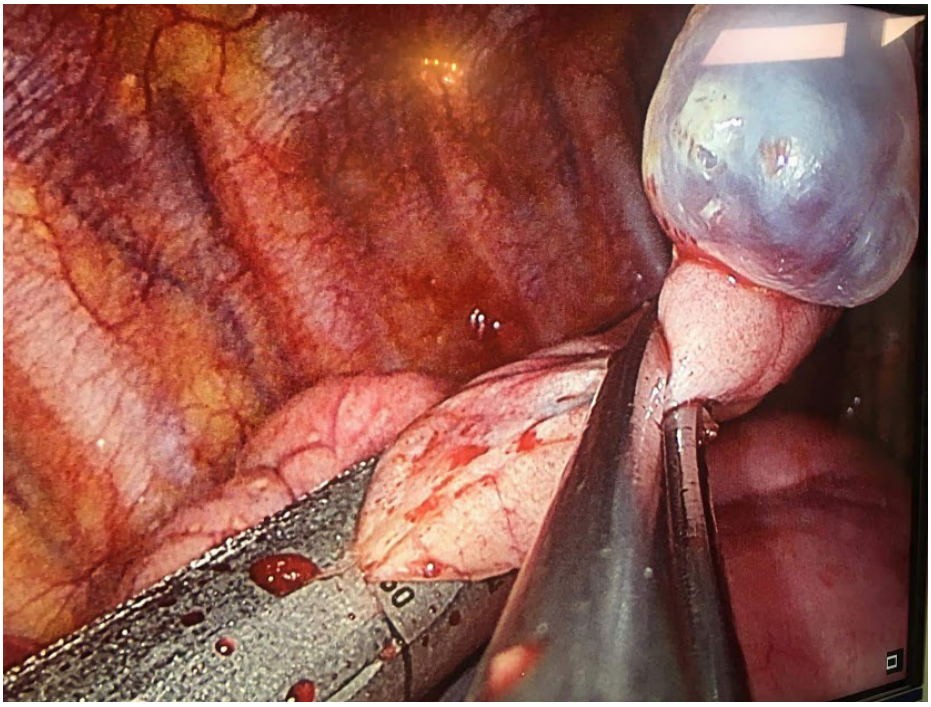

Figure 2. Intraoperative image of wedge resection applied to parenchymal bulla.

2.2. Mediastinal Pathologies

Today, the applications of awake VATS in mediastinal pathologies are limited to mass biopsy and lymph node dissection/sampling. Although some case reports of the use of the awake VATS method in the excision of well-circumscribed small sized mediastinal masses have been published (Figure 3), it has not become widespread due to the anatomically risky structures of the anterior and middle mediastinum that are open to complications.

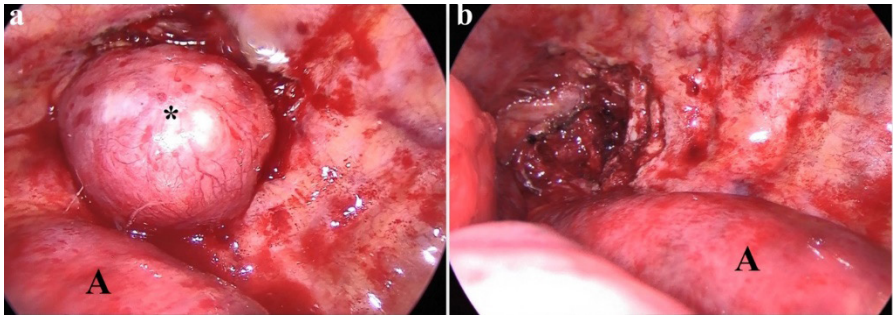

Figure 3. Intraoperative images of the left posterior mediastinal mass excision with VATS. Asterisk indicates mediastinal mass. A: Aorta.

2.3. Parenchymal Diseases

A wide range of awake VATS applications have been reported, from interventions such as parenchymal biopsy and parenchymal nodule excision where wedge resection would be sufficient, to anatomical lung resections such as segmentectomy and lobectomy.

Awake VATS wedge resection has become a generally accepted approach for parenchymal biopsy especially in indetermined interstitial lung diseases. In this patient group, the complication risks of endotracheal intubation and mechanical ventilation are higher than in patients with healthy lung tissue therefore, the awake VATS approach should be kept in mind when surgical biopsy is required.

Another procedure in which the awake VATS approach has been successfully applied is metastasectomies (Figure 4). It has been shown in the literature that metastactomies performed with the awake VATS approach are associated with less overall operative time, lower post-operative morbidity rate and milder impact on inflammatory system.

Among the awake VATS applications, the most interesting and praiseworthy application is anatomical lung resections. Gonzales-Rivas, one of the pioneers in this field, reported the first awake uniportal VATS lobectomy case in 2014. In the following years, encouraging series of segmentectomy and lobectomy performed with awake VATS from different centers were published.

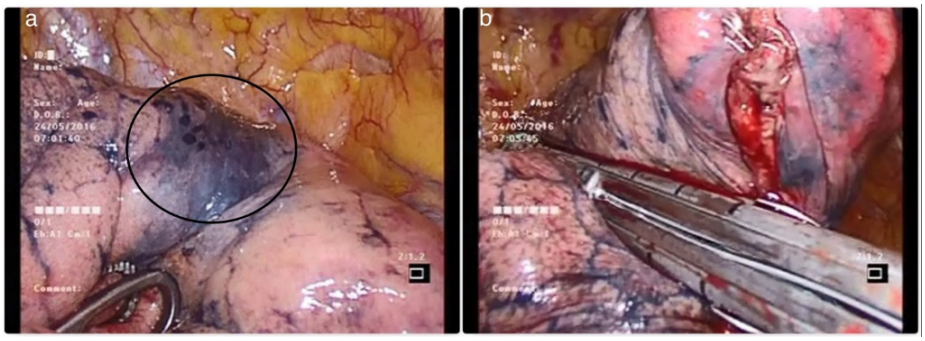

Figure 4. Intraoperative image of wedge resection performed after methylene blue marking. The portion of lung parenchyma marked with methylene blue is shown in the circle.

It seems that with increasing experience, the awake VATS method in lung resections will become an important part of daily practice.

3. Patient Selection And Contraindications

The common emphasis in relevant studies is the importance of patient selection. Undoubtedly, patient selection for the awake VATS method will require the collaboration of a team including pulmonologists, thoracic surgeon and anesthesiologist. Patients should be evaluated in detail in terms of airway problems that may cause difficulty in spontaneous breathing or intubation, accompanying medical conditions (obesity, scoliosis, chest wall deformity etc.) and personality traits (i.e., anxiety level, cooperativeness, and mental state).

Awake VATS can be chosen for patients considered contraindicated for general anesthesia due to their low pulmonary capacity. However, all patients will inevitably experience hypoventilation due to the iatrogenic pneumothorax created during the awake VATS procedure. As a result, patients are predisposed to carbon dioxide retention during surgery. Therefore, the degree of respiratory failure is important for patient selection. Wang et al. reported that lung resection with awake VATS is safe in patients with insufficient pulmonary capacity. However, in patients with severe obstructive respiratory disorder (FEV1 < 30%), awake VATS will be risky. In addition, awake VATS is considered contraindicated in the presence of obesity, which causes low tidal volume. In the study of Hung et al., obesity (BMI>25) was found to be a risk factor for conversion to intubation during awake VATS.

As a result, in patient selection, the team should analyze the patient's data well and make a profit-loss calculation for each patient.

4. Anesthesia Techniques And Airway Management

4.1. Anesthesia

Cardiotoxicity, hepatotoxicity, aspiration pneumonia due to neuromuscular blockade, and postoperative nausea and vomiting are among the complications of general anesthesia. The use of regional anesthesia methods is one of the most important advantages of awake VATS.

Intercostal nerve block (INB), paravertebral block, serratus anterior plane block, and thoracic epidural anesthesia (TEA) are the most commonly preferred anesthesia methods in awake VATS procedures.

4.1.1 Intercostal Nerve Block (INB)

The intercostal nerves innervate the major parts of the of the chest and blockage of these nerves provides effective analgesia in surgical interventions of the thoracic region. Compared to other regional anesthesia types, the risk of complications is lower, and it is easier to apply.

INB can be applied percutaneously with the guidance of USG, or it can be applied intrathoracically under direct vision with a thoracoscope (Figure 5 and 6).

Compared with TEA, its greatest advantage is that it does not have the risk of spinal cord injury and does not cause hemodynamic instability.

It can be applied as a one-time application with 20–22-gauge needle or continuously by placing a 18–20-gauge catheter.

Bupivacaine, lidocaine or ropivacaine can be preferred as a local anesthetic agent.

3-5 cc injection is sufficient for each level. Epinephrine would be added to slow the systemic absorption and increase the local effect. The most commonly preferred agent is bupivacaine, with a duration of action of approximately 6-12 hours. If continuous blocking is performed using bupivacaine 0.25%, a loading dose of 0.3 mL/kg followed by an infusion of 0.1 mL/kg/h often provides effective analgesia.

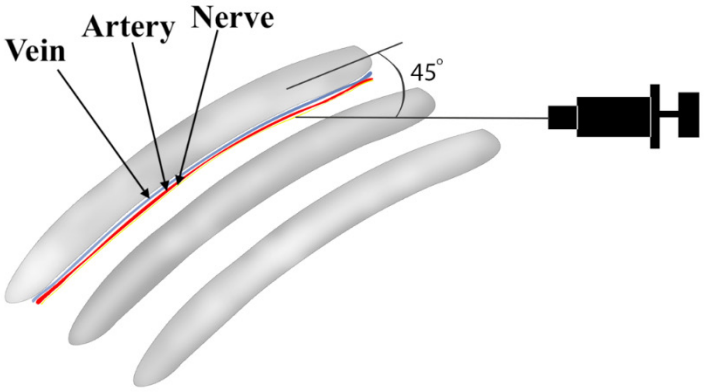

Figure 5. Injection is applied at an angle of 45 degrees to target the intercostal nerves located in the "sulcus costae" under the ribs.

4.1.2 Thoracal Paravertebral Block (TPNB)

TPNB is a regional anesthesia method that provides unilateral segmental somatic and sympathetic nerve block by targeting the emerging region of the spinal nerves from the intervertebral foramen (Figure 7). Unlike intercostal nerve blockade, the injected anesthetic agent can spread to the epidural area medially and may show distribution in the caudal and cranial directions. It is difficult to predict the distribution pattern and the levels it will affect in high volume applications. Therefore, multiple injections, with a small amount to each level, are preferred to large volume injections to a single level. It has been reported that 10% of patients develop segmental contralateral nerve involvement due to possible epidural spread.

The two most important anatomical markers to consider in application of TPNB are the transverse vertebral process and the superior costotransverse ligament. The thoracic paravertebral space is the area where the anesthetic agent should be injected. It should be kept in mind that pneumothorax may develop secondary to injury to the pleura and/or lung if adequate care is not taken.

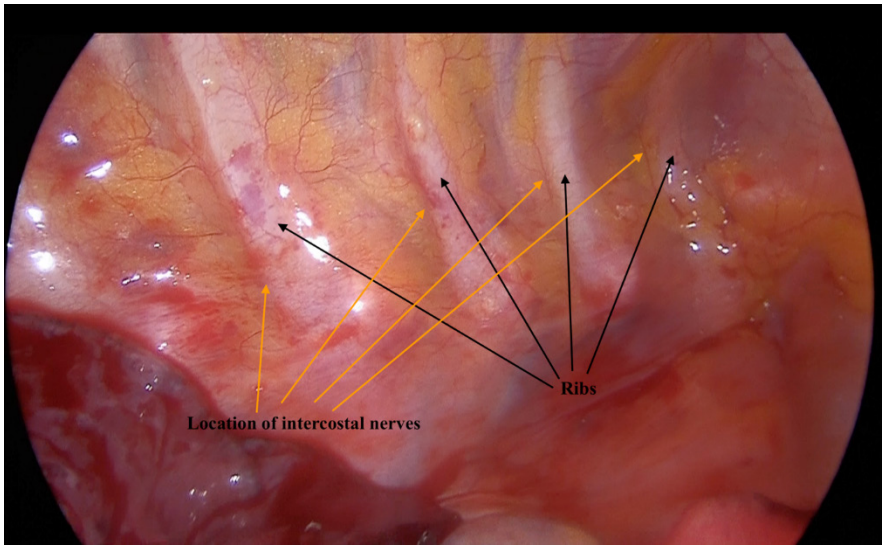

Figure 6. Intraoperative view of the ribs and intercostal spaces.
ICB can also be performed intraoperatively with the aid of a catheter.

4.1.3. Serratus Anterior Plane Block

The development of the features of ultrasonography devices and the increase in the image quality obtained have led to the development of new analgesic block techniques. Serratus anterior plane block is new ultrasound-guided regional anesthesia technique and is an effective method for analgesia of the ipsilateral chest wall. In this technique, the block of the lateral cutaneous branches of the intercostal nerves, the long thoracic nerve and the thoracodorsal nerve in this plane is targeted by injection into the plane between the serratus anterior and latissimus dorsi muscles from the axillary region (Figure 8).

Studies in the literature on chest wall nerve blocks, including the pectoral nerve block and serratus anterior plane block, are limited. However, available data suggest that effective pain control can be achieved with this method.

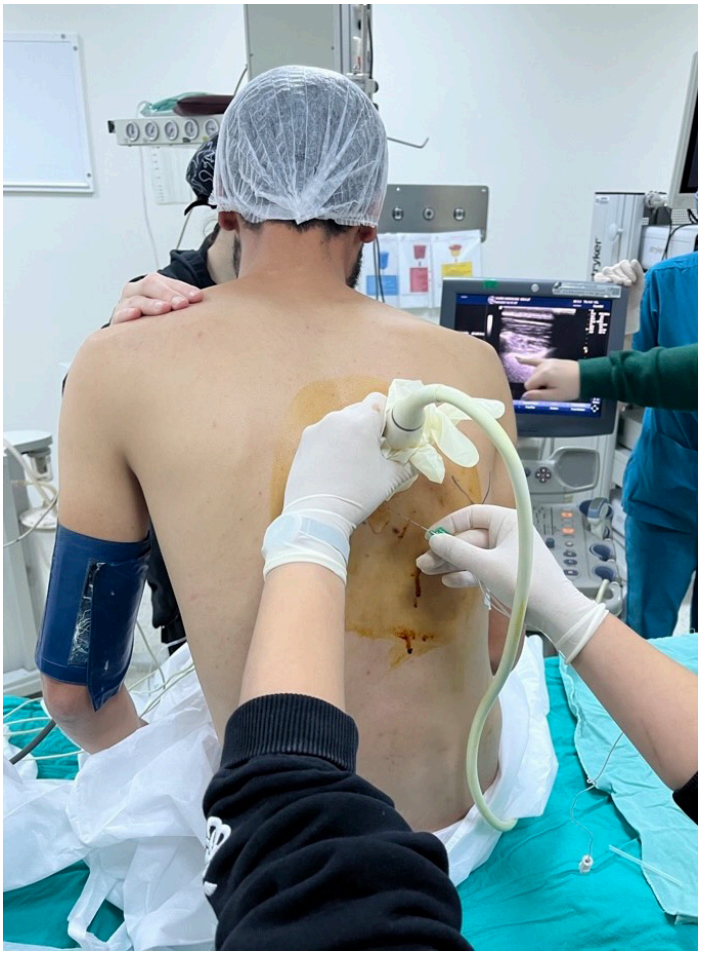

Figure 7. USG-guided TPNB application.

4.1.4. Thoracic Epidural Anesthesia (TEA)

The clinical conditions in which epidural analgesia is applied are in a wide spectrum including intraoperative and postoperative analgesia, management of chronic and acute pain. The preferred epidural catheter level is T3-T6 to block sensory innervation in the thoracic wall without affecting the diaphragm muscle. Studies have shown that TEA is associated with reduced postoperative complication rates when compared to systemic opioids. TEA, which provides effective analgesia, is generally cited as a safe method. However, the variety and severity of complications that may develop are higher than in other regional analgesia methods. The most feared complications are epidural bleeding,

spinal cord injury, subarachnoid block and infection. In addition, hypotension, bradycardia, and arrhythmia may be seen after TEA due to sympathetic block. However, providing effective analgesia with TEA and being a relatively safe method have made it frequently preferred in awake VATS procedures.

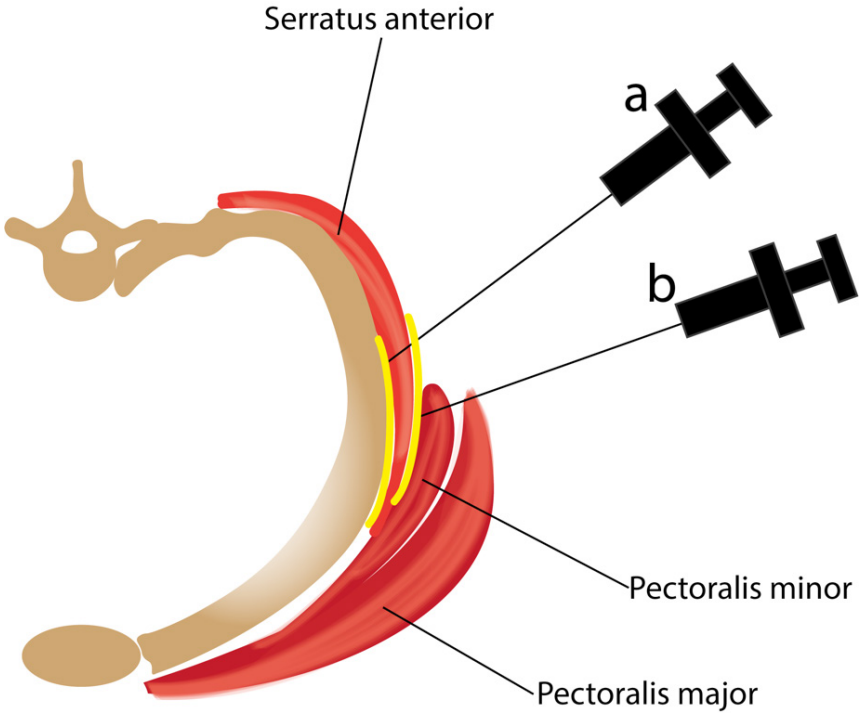

Figure 8. Serratus anterior plane blocks are effective regional analgesia methods applied under the guidance of USG.
a. Sub-serratus plane block.
b. Supra-serratus plane block.

4.2. Airway Management

Sedative medication is often combined with anesthetic methods in order to reduce the patient's anxiety and increase the surgeon's comfort. Low-dose remifentanil or propofol infusion are often the agents of choice. The respiratory rate of the patient should be closely monitored and doses that will cause respiratory depression or hypoventilation should not be exceeded.

Spontaneous breathing can usually be assisted with a nasal mask, laryngeal mask airway (LMA), high-flow nasal cannula (HFNC), or oropharyngeal cannula.

4.2.1. Nasal Cannula, Simple Mask, And Mask With Reservoir

A decrease in vital capacity occurs due to iatrogenic open pneumothorax in the awake VATS procedure. Therefore, supplemental oxygen is administered in all cases.

The nasal cannula is one of the most commonly used devices for oxygen support in the spontaneously breathing patient. The nasal cannula can provide oxygen supplementation up to 6 lt/min. 4-6 lt/min of oxygen corresponding to 36-44% FiO2 is sufficient for most patients undergoing awake VATS.

Another alternative is the application of oxygen by mask. While simple masks provide 40-60% FiO2, up to 80% FiO2 can be delivered with reservoir masks. Therefore, reservoir masks are useful in patients with underlying parenchymal pathology such as interstitial lung disease during awake VATS.

4.2.2. LMA

LMA is a supraglottic airway device developed as an alternative to balloon-valve-mask (BVM) ventilation for use in emergency conditions. It is superior to BVM in allowing the practitioner to empty their hands and cause less gastric inflation. Due to its ease of use, it is a good alternative to orotracheal intubation in short surgical procedures.

Videothoracoscopic surgical procedures performed with LMA fall into the category of non-intubated general anesthesia rather than awake VATS. It is an alternative to awake VATS as it allows general anesthesia to be applied without the need for tracheal intubation and prevents cough, pain and anxiety attacks. However, if it is not placed well, insufficient respiration, gastric inflation and aspiration risk are the disadvantages of this technique.

4.2.3. HFNC

HFNC is a method that allows high-concentration (up to 100%) heated and humidified oxygen to be delivered transnasalally with a high flow rate (up to 60lt/min). It can be used in hypoxic respiratory failure, in case of hypoxia due to thoracic trauma, or to provide oxygen saturation before or during invasive procedures. It offers high amounts of oxygen to the use of patients in a more comfortable way. HFNC may be preferred to ensure adequate oxygenation during the awake VATS procedure, especially in patients at risk of hypoxic respiratory failure due to underlying lung pathology.

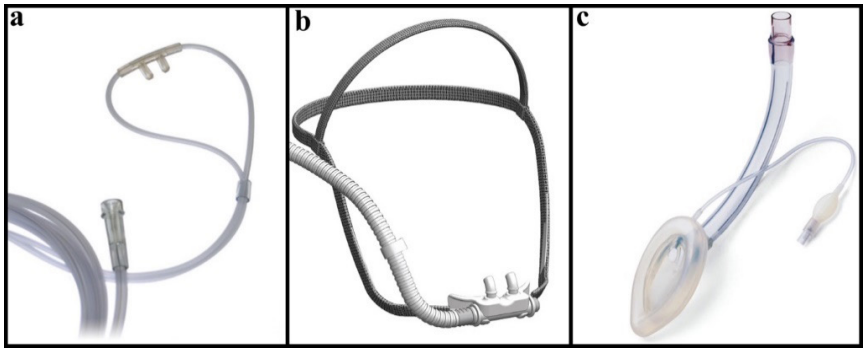

Figure 9. Oxygen delivery methods and airway management vary according to the patient's oxygen requirement, sedation status, and expected surgical intervention time. The nasal cannula (a), HFNC (b) and LMA (c) are commonly used instruments in awake VATS.

5. Surgical Techniques

The surgical procedure in awake VATS is similar to that of conventional VATS. The patient is in the lateral decubitus position. Port numbers and locations are determined according to the nature of the procedure and the surgeon's preference (Figure 10 and 11).

Vagus nerve infiltration can be performed intraoperatively, as manipulation of the hilar structures may trigger the cough reflex in the patient (Figure 12). In addition, inhalation of 2% nebulized lidocaine before the operation is among the recommendations to suppress the cough reflex. Unnecessary manipulation of the lung and excessive dissection of mediastinal structures should be avoided. The surgeon should be in close communication with the anesthesia team during the procedure.

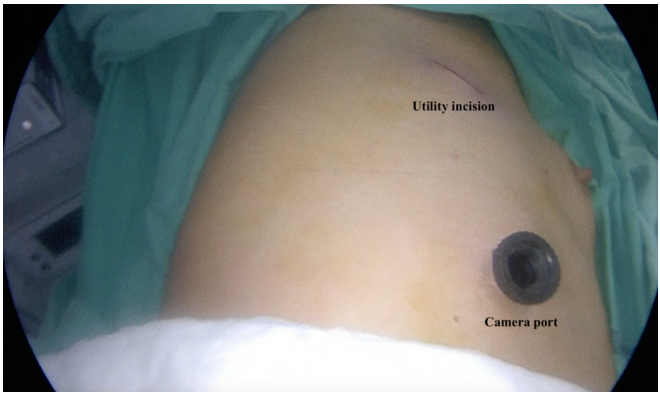

Figure 10. The image shows the patient in the lateral decubitus position. VATS was applied using two ports.

At the end of the operation, there are some maneuvers that can be applied to ensure the re-expansion of the lung:

- The patient can be ventilated manually with a mask.
- If the patient has LMA, positive pressure ventilation can be applied.
- If HFNC is applied, the positive pressure effect can be utilized by maximizing the flow rate.
- Negative suction can be applied through the port or chest tube to achieved re-expansion of the lung.

6. Future

The main instinct of minimally invasive surgery is to achieve similar or better results with less tissue trauma and less disruption to normal physiological functioning. This is the basic instinct behind awake VATS applications, as was the advent of videothoracoscopic approaches. Shared surgical results of awake VATS are promising. As experience increases in

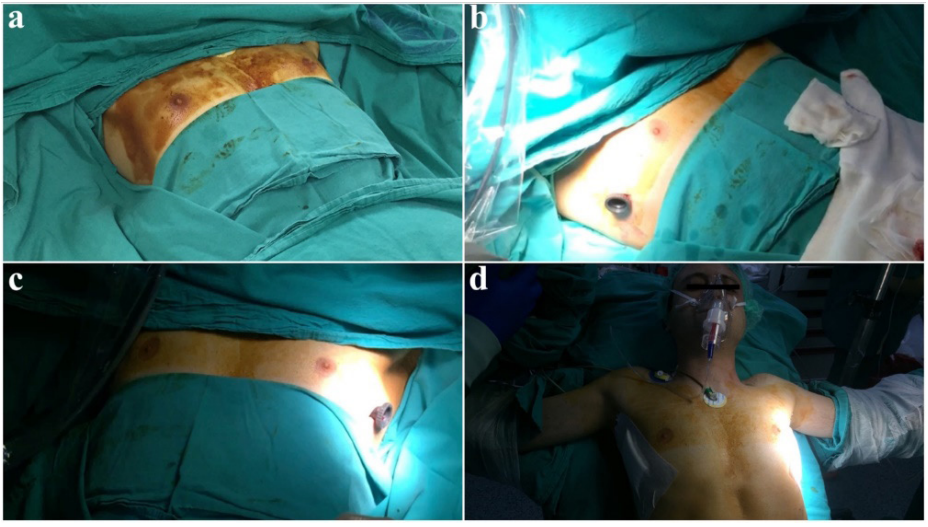

Figure 11. Images of bilateral thoracic sympathectomy operation performed with the awake VATS technique are shown. The patient, who was administered thoracic epidural anesthesia, was in the supine position (a, b, c). During the operation, oxygen inhalation was applied to the patient with a mask (d).

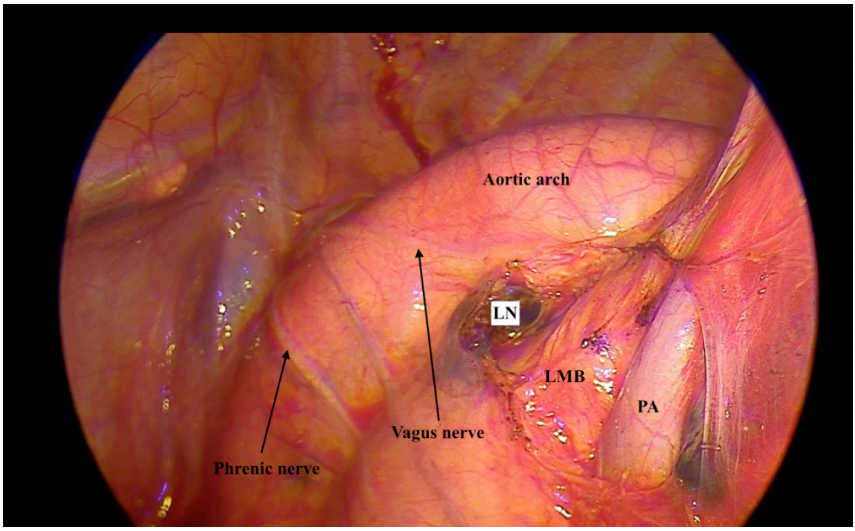

Figure 12. Intraoperative image of left sided VATS procedure.
Cough reflex can be suppressed temporarily by the infiltration of the vagus nerve.

LMB: Left main bronchus, LN: Lymph node, PA: Pulmonary artery.

awake VATS, which requires close communication between the anesthesia and surgical team, it will be preferred in more complicated procedures. The development of new pharmacological agents and anesthesia techniques that provide sedation and analgesia without depressing respiration will allow the use of the awake VATS method in more complicated and time-consuming surgical procedures. Today, anatomical lung resections can be performed with awake VATS in experienced centers. The widespread use of awake VATS in anatomical resections performed for the treatment of lung cancer will provide the chance of curative resection in patients who are considered high-risk for general anesthesia and one-lung ventilation.

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CHAPTER IX

DEEP BRAIN STIMULATION SURGERY

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1. Introduction

Deep brain stimulation *(DBS)* surgery is probably the fastest growing field of neurosurgery. Its efficacy has been proven in Parkinson's disease (PD), essential tremor and dystonia, and its use in a range of neurological and psychiatric disorders is also being investigated. Thalamic DBS was approved by FDA in 1997 for the treatment of essential tremor and Parkinson's disease-associated tremor. In 2003, sub-thalamic nucleus (STN) and globus pallidus internus (GPi) DBS were also approved by FDA for the treatment of Parkinson's disease. DBS has been in clinical use since 2003 in primary generalized and segmental dystonia, and in obsessive-compulsive disorder since 2009 with FDA's "humanitarian device exemption" status.

The modern form of DBS has been introduced in 1987 by Benabid and Pollak from Grenoble, France in patients with tremor. Deep Brain Stimulation (DBS) was first introduced by Benabid et al. in 1987 as an alternative to the surgical treatment of Parkinson's Disease (PD). The first application was made to the ventral-intermediate nucleus of the thalamus. The sub-thalamic nucleus, medial globus pallidus and ventral intermediate nucleus of the thalamus are the most effective target areas for deep brain stimulation in movement disorders and Parkinson's patients.

In the following priod, DBS began to replace thalamotomy in the treatment of tremor. It was also reported by the same group in 1993 that bilateral sub-thalamic nucleus DBS could reduce the dose of dopaminergic drugs in advanced Parkinson's disease. As a result, STN – DBS has replaced other surgical procedures for the surgical treatment of Parkinson's disease in the nineties.

Sub-thalamic nucleus stimulation, has been developed in the last decades and is positioned as the most successful region for application. Additionally, deep brain stimulation has been utilized in motion disorders and motor complications due to the use of levodopa, hence improvement of tremor.

Stimulation of the ventral intermediate nucleus of the thalamus is effective for tremor but not for other symptoms of Parkinson's patients. Deep brain stimulation of the pars interna of the globus pallidus and the sub-thalamic nucleus provides improvement not only in tremor but also in other main findings of Parkinson's patients. As a result of clinical studies, bilateral stimulation of the sub-thalamic nucleus has been found to be a good target area for clinical symptoms. Bilateral sub-thalamic nucleus stimulation is a suitable surgical method for patients with severe immobility and on/off movements, off dystonic posture, and dyskinesias due to levodopa.

Deep brain stimulation is high-frequency stimulation of target tissues without causing any damage to the brain. Frequencies between 50 and 180 Hz are generally preferred for stimulation. In deep brain stimulation, a small electrode is placed in related brain regions via the stereotactic method. A continuous high – frequency stimulus is given via a pulse generator placed under the skin just below the clavicle, connected to this electrode. In rare cases, the stimulation of sub-thalamic nucleus, creates undesirable conditions such as over – stimulation of the substantia nigra.

The mechanism of deep brain stimulation has not been fully elucidated. However, it is thought to improve motor activities by neutralizing abnormal brain activity and improving brain functions in target areas. Suppressing the pathological pallidal output with high – frequency stimulation, preventing depolarization, inhibiting gama – aminobutyric acid (GABA) channels that play a suppressive role from the external part of the glabus pallidus, draining neuronal energy. Briefly, synaptic insufficiency, suppression of the activation of excitatory neurotransmission are expressed as possible mechanisms of deep brain stimulation.

Studies with bilateral sub-thalamic nucleus stimulation have reported improvement in all parkinsonism parameters *(tremor, rigidity, bradykinesia, etc.)* after surgery. In addition, it is stated that there is an average 50% increase in the quality of life of patients.

The most important advantages of deep brain stimulation can be elaborated as its favorable tolerability profile compared to lesion-based applications, bilateral application chance, and reversible post – operative application in order

to improve symptoms or minimize side effects. The disadvantages can be stated as the risk of hemorrhage with electrode insertion, mechanical inadequacies related to the instrument due to placement and battery changes, infection, high cost and difficulty in application.

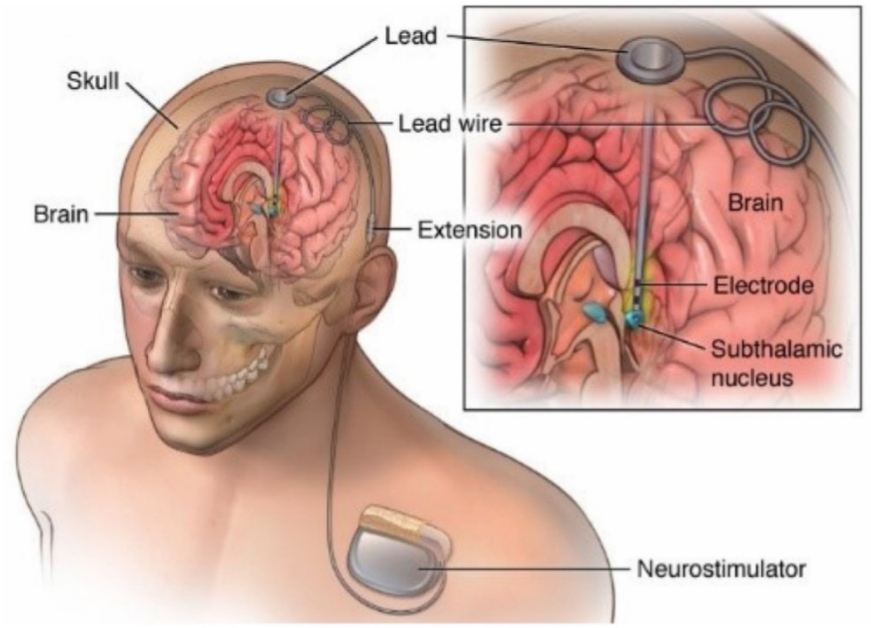


Figure 1: The physiological mechanism of action of deep brain stimulation

2. The Physiology of Deep Brain Stimulation

Deep brain stimulation is a surgical treatment for various neurological diseases. In DBS surgery, electrical stimulation is transferred to the target area via implanted electrodes. To date, the mechanism of action of DBS was not clear. It has been suggested that DBS acts through the mechanism of depolarization blockade, by releasing local inhibitory neurotransmitters and activating inhibitory neurons that antagonize dopamine action. Thus, DBS stabilizes the chemical composition of the basal ganglia, reducing motor fluctuations and alleviating the symptoms of PD. DBS is widely used as it is reversible and the stimulation parameters can be adjusted by neurologists on a case-by-case basis.

Deep brain stimulation entered clinical practice nearly 40 years ago and is currently the standard treatment for Parkinson's patients experiencing motor complications. There are numerous studies reporting changes in various non-

motor symptoms, as well as improvement in motor symptoms, in Parkinson's patients after the administration of STN – DBS. Psychiatric symptoms such as depression, apathy, anxiety, and impulsivity may worsen or improve depending on electrical stimulation parameters, the location of stimulating contacts in the STN, and post-surgical drug changes.

Movement disorders that benefit from DBS result from dysfunction in neuronal circuits composed of cortical and subcortical components (motor basal ganglia in Parkinson's and dystonia, cerebello-thalamo-cortical circuits in Parkinson's tremor and essential tremor). The motor circuits of the basal ganglia play a role in motivation and measure of movements, selection of appropriate actions and inhibition of unwanted movements.

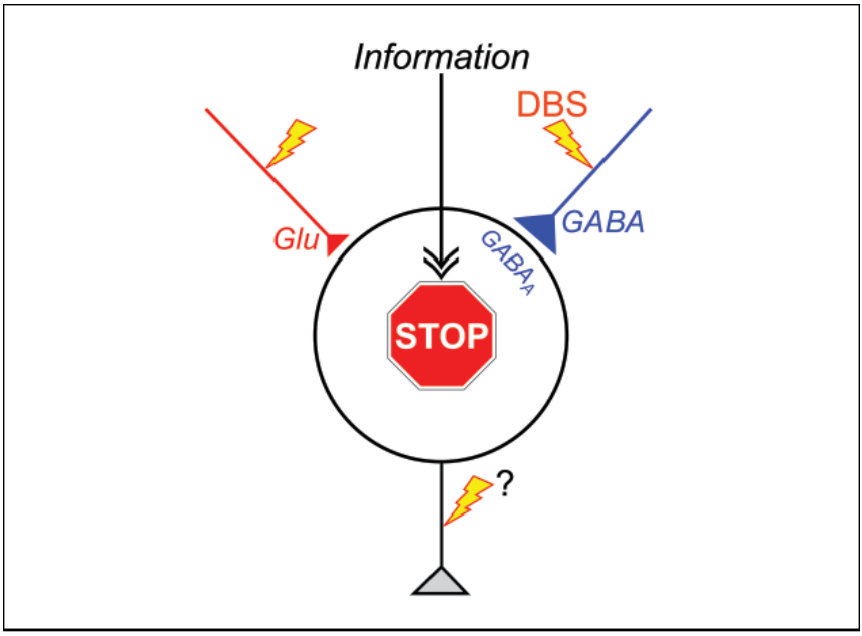


Figure 2: Mechanism of action of deep brain stimulation

GPi exerts an inhibitory control over thalamocortical excitation. The direct pathway facilitates thalamocortical excitation by inhibiting GPi hence the indirect pathway has an opposite effect. The outcome is scaling and selection of appropriate motor programs of voluntary movements, inhibition of undesired movements.

There is a third hyperdirect pathway extending from the cortex to the STN, and the effect of this pathway on thalamocortical conduction is similar to that of the indirect pathway. Only this pathway is faster as it bypasses the

striatum and is involved in the preparatory phase for the selection of appropriate movement.

Striatal dopamine released from the nigrostriatal pathway acts as a neuromodulator and creates an inhibitory effect on GPi/SN by facilitating cortico-striatal inputs in the direct pathway and inhibiting the indirect pathway, ultimately facilitating thalamic excitation on the cortex.

Consistent with this model, high-frequency stimulation of STN or GPi is believed to act similarly to surgically created lesions in pallidotomy/ subthalamotomy by inhibiting output in target nuclei. Several mechanisms have been proposed to explain the inhibitory effects of high – frequency stimulation.

Although the direct and indirect pathway model may reveal the underlying pathophysiology of some movement disorders and is supported to some extent by empirical evidence. Paradoxes have been observed in clinical practice that suggest that the model is over – simplified. This model predicts that creating a pallidal lesion will relieve Parkinsonism and result in a hyperkinetic state, but not hyperkinesis in real life.

Electrophysiological studies and local field potential measurements in patients have proven that Parkinsonian status is associated with abnormal bursts and hypersynchronous activity in nodes in the motor circuit (such as GPi and STC). Vibrations in the 10-25 Hz range (beta band) are seen in the uncontrolled Parkinson's condition and are replaced by more asynchronous gamma band (60-80 Hz) vibrations, accompanied by symptom relief with levodopa therapy. Based on such electrophysiological and clinical observations and computer models, the firing patterns of basal ganglia neurons are believed to be as important as or more than firing rate in shaping the final motor output. While beta band oscillations are associated with rigidity and bradykinesia, tremor in PD does not correlate with the severity of nigrostriatal dopaminergic denervation, unlike the other two.

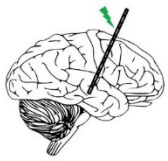
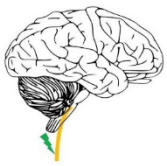
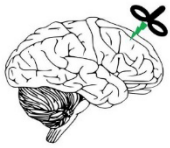
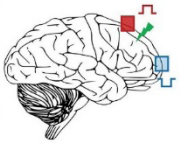
	Deep Brain Stimulation (DBS)	Vagus Nerve Stimulation (VNS)	Rythmic Transcranial Magnetic Stimulation (rTMS)	Transcranial Direct Current Stimulation (tDCS)
TYPE				
TARGET	Midbrain Thalamus Pallidum Striatum	Vagus Nerve	Right or left dorsolateral prefrontal cortex or Right or left primary motor cortex	Left dorsolateral prefrontal cortex or Posterior parietal cortex
CURRENT	Low (8-30 Hz) or high frequencies (50-250 Hz) 1-20 V voltages	30 Hz 1.5 mA intensity	Single or repeated sessions 5-20 Hz	20 minutes sessions (single or repeated) 1-2 mA intensities
INVASIVE	Yes	Moderately	No	No

Figure 3: Different Neuromodulation Therapies with different levels of invasiveness

Anomalies of the cerebellothalamocortical circuit are associated with tremor, which responds well to thalamic DBS, which regulates this circuit. Impaired firing patterns and abnormal levels of synchrony in various basal ganglia diseases lead to abnormal flow of information in these circuits, resulting in pathological function changes in the thalamocortical and brainstem networks to which basal ganglia outputs are projected. Thus, DBS acts as an "information lesion" and filters the abnormal flow of information. In this case, it may explain the efficacy on hypokinetic disorders as well as hyperkinetic disorders.

DBS is a whole consisting of interdisciplinary decisions of patients, families, neurologists, neurosurgeons and psychiatrists. Everyone involved in the process, including patients, should have realistic expectations after surgery. Patients should be aware that DBS does not completely cure the disease, but mainly optimizes motor symptoms and therefore quality of life.

A detailed evaluation is required to determine whether the patient will benefit from DBS. First, the diagnosis of idiopathic Parkinson's disease must be confirmed because other Parkinson's syndromes often do not respond to DBS. In addition, the patient's current and past anti-Parkinsonian medications and their dosing schedules should be carefully reviewed. Response to dopaminergic medication (levodopa) should be retested, as improvement in motor symptoms after the 'L-DOPA challenge' is one of the few known predictors of clinical

outcomes after DBS. There is a compelling need for an investigator independent approach and the development of a goal with accuracy to present symptoms and approximate post-surgical improvement that can still be targeted by DBS.

DBS is typically administered in PD during the 11 – 13 year disease duration, during the deterioration of motor complications that have detrimental effect on quality of life (QoL) in the majority of patients. Recently it was shown that, DBS has denoted beneficial effects at least in the younger group of patients with lower surgical risk, better than best medical treatment if these patients are treated earlier than this disease duration.

3. Patient Selection Criteria in Deep Brain Stimulation

US Food and Drug Administration ("The United States Food and Drug Administration" – FDA) has approved the indication of DBS in movement disorders such as PD, dystonia and essential tremor (ET). DBS is currently the standard of care for patients with Parkinson's disease who experience motor complications with levodopa therapy. Apart from this, some well-selected levodopa unresponsive tremor cases of PD also may respond well to DBS.

Careful patient selection is very important to obtain good results with DBS, because only levodopa-responsive symptoms are likely to respond to DBS (excluding tremor). The motor response to levodopa should be documented before selecting Parkinson's patients for DBS. PH – dementia coexistence is an absolute contraindication hence, active depression, psychosis, and other neuropsychiatric symptoms should be corrected and stable remission should be achieved before surgery.

Advanced age is a relative contraindication and in many centers, the age of 70 is taken as a "cut-off" for the decision of advanced age. Individuals over 70 years of age are often associated with faster progression of PH, steeper decline in cognition, greater burden of comorbidity, and greater brain atrophy.

A minimum of 4 years of motor symptom duration is recommended to confidently accept a clinical diagnosis of PH after excluding atypical Parkinsonian syndromes, and documenting a good levodopa response.

Deep brain stimulation (DBS), an adjustable stimulation, is a reversible procedure that provides a beneficial effect for the patient. The durability, safety, efficacy, and cost-effectiveness of DBS for essential tremor and Parkinson's disease are well established. It is known that DBS will bring positive surgical results and feedback with a multidisciplinary team such as neurosurgery,

neurology, neurophysiology, psychiatry, neuroanesthesiology, neuropsychology and physical therapy and rehabilitation. Furthermore an experienced nurse is also an integral part of the team. For physicians and healthcare professionals dealing with neuroscience it will be useful to summarize footnotes and checklist for patients with movement disorder in the preoperative period.

Selecting suitable candidates for DBS is very important. Criteria of DBS should aim to identify candidates who will gain the greatest benefit from the intervention physically, cognitively and emotionally and also tolerate surgery and maintain their own post – operative care.

Screening potential candidates in this way by experienced DBS teams means that each member contributes with their expertise to the entire team, and in this context, the team specializes in assessing the diagnosis of the disease and the patient's cognitive and psychiatric condition.

Being able to predict which patients are poised to achieve the best results becomes important because, first, the high costs of the procedure can be a limiting barrier for delivering treatment to all patients, and second, inappropriately selected patients may not derive significant benefit from treatment. Having a well – defined patient selection procedure that includes factors known to contribute to success will maximize clinical outcomes for DBS.

Factors such as age, motor symptoms, response to levodopa, neuro – psychological and psychiatric status of the patient, presence of comorbid diseases, quality of life, substance abuse or addiction are extremely important in determining the right candidates.

These neuro – psychological events may rule out DBS for some patients and indicate a more comprehensive consideration of the patient as a candidate. Other considerations in selecting patients who will do the "best" include considerations of family support, commitment, and expectation. Since patients may need to remain conscious during surgery to participate in functional mapping studies. It is important for patients and caregivers to adhere to medication management and treatment regimen during pre– and post – operative follow-up, as large amounts of time and energy may be spent on screening appointments.

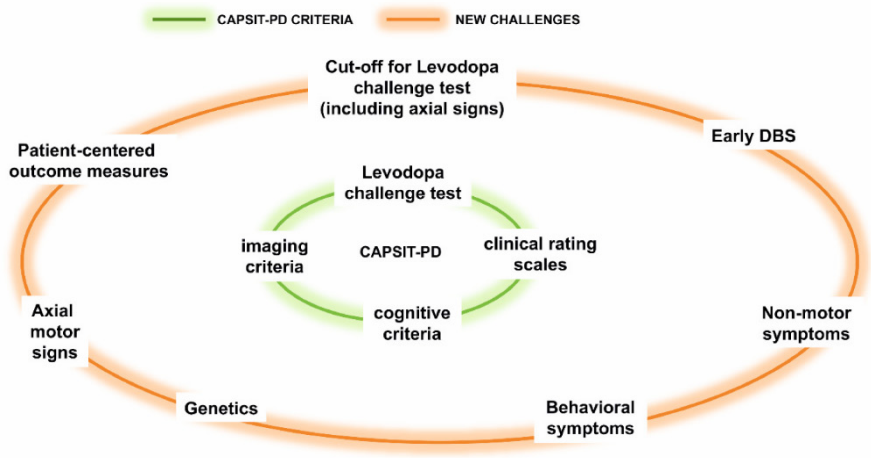


Figure 4: Deep brain stimulation patient selection criteria for Parkinson's Disease

Maximizing the potential for success of DBS will also involve managing patient expectations. Patients should have realistic expectations about the procedure and the probability of failure and understand the impact of the intervention on their symptoms. Although patients with different diseases have different expectations about what kind of symptoms will improve with DBS, neither patients nor their families should know that DBS is not curative and should not enter into promising expectations.

There are some common misconceptions should be cleared from the start of the discussion. DBS aims to alleviate the symptoms of the disorder and improve overall quality of life in daily tasks. If these issues are not fully discussed, patients risk disappointment and potential perceived failure of treatment. It is suggested that clearly defined conscious education about expected successes and failures can help manage expectations in patients and families. However, clinical studies define overrated expectations for patients. Patient expectation should be evaluated and it should be foreseen that DBS for neuropsychiatric conditions may be prominently included in patient selection criteria for future uses.

Table 1: *Checklist for Preoperative DBS Candidate Parkinson's Disease*

- *The diagnosis of PH must be definite*
- *No early/mild PH*
- *At least 5 years must have passed since symptom onset*
- *No significant postural instability in the first 3 years from the onset of symptoms*

- *No early freezing in the first 3 years*
- *No drug-independent hallucinations in the first 3 years*
- *No dementia precedes motor symptoms in the first year*
- *There should be no supranuclear gaze palsy*
- *No upper motor neuron findings on examination*
- *No severe, symptomatic dysautonomia independent of drugs*
- *The patient has features that respond very well to DBS (rigidity, tremor, bradykinesia, motor fluctuations) and low-response features (speech and swallowing disorder, micrography, postural instability, frostbite) should be reviewed.*
- *Medications must have been used in the optimum regimen and dose before DBS*
- *Response to dopaminergic treatment should be observed (at least 30-33% improvement in UPDRS III score with L-dopa test)*
- *The patient should not have dementia*
- *The patient should not have severe depression, active hallucinations, delusions, psychotic symptoms not induced by drugs*
- *Patient compliance should be sufficient*
- *Comorbid diseases should not be a contraindication for the neurosurgeon.*
- *His family and other relatives should be able to provide support after DBS*
- *Expectations of the patient and their relatives should be realistic.*
- *No abnormal brain imaging other than changes related to PD*

Table 2: *Checklist for the Preoperative DBS Candidate Essential Tremor Patient*

- *The diagnosis of ET must be definitive*
- *Symptoms must lead to severe functional disability*
- *No response despite adequate pharmacological treatment*

Table 3: *Checklist for DBS Candidate Dystonia Patient in the Preoperative Period*

- *The diagnosis of dystonia must be definite*
- *No response despite adequate pharmacological treatment*
  - *Botulinum toxin treatment must have been tried by at least 3 different specialists*
  - *At least 900 mg/day dopaminergic treatment must have been tried*
- *The following should also be considered:*

o *Primary dystonia responds much better than secondary dystonia (except tardive dystonia)*

o *Those with short disease duration and primary generalized dystonias give better results*

o *Those with abnormal brain imaging have a weaker response*

o *Limb dystonia patients respond better than midline dystonia patients*

o *Surgery should be considered before skeletal deformities occur and fixed posture develops.*

4. Complications of Deep Brain Stimulation

DBS – related complications are divided into the following 3 different categories.

1) *Those associated with the surgical procedure (Category 1 includes intracranial hemorrhages, infections, epilepsy and air embolisms)*

2) *Those associated with a problem with the DBS device and its connections (Category 2 includes device failure includes electrode breakage, skin erosion on the implantable pulse generator or electrical wiring, and associated infections. This category also includes the electromagnetic associated complications surrounding patients.)*

3) *Those associated with DBS-stimulated neuronal structures and networks (Category 3 includes psychiatric and cognitive dysfunctions and an increased risk of suicide after DBS.)*

4.1. Surgical Complications

When we look at the results of various series in general, the rate of early surgical complications varies between 1% - 15%. The main ones are wound infection, sterile seroma, intracerebral hematoma, foreign body reaction, central nervous system infection. In addition, impedance disturbances, electrode fracture and hardware-related wound site problems are between 2.5% - 50%. Surgical complications are generally related to the surgical technique, the experience of the surgical center or the working methods of the procedure.

4.2. Unresponsiveness to Deep Brain Stimulation

Appropriate patient selection for good response to deep brain stimulation, correct surgical technique, optimum stimulation programming level and medical treatment should be sufficient. These parameters should be reviewed

when the expected response from deep brain stimulation is not obtained. Appropriate patient selection is extremely important to achieve successful results.

Failure in the initial diagnosis or selection of patients who are not suitable for surgery may present as DBS unresponsiveness. Accurate surgical targeting is another important parameter for optimal response. Incorrect placement of the electrode may be due to inadequate localization techniques, or it may develop due to the lack of training or experience of the practitioner. Checking the the electrode placement is important and a post-surgical imaging should be performed. Other reasons may be due to hardware-related cable or connection breaks, short circuits, battery life or edema, infection, erosion of the tissue. Impedance measurements must be made during programming. In cases where there is no problem in patient selection and surgical technique, the appropriateness of stimulation and medical treatment should be reviewed.

DBS can be planned for an alternative target when no effect can be achieved, but it should be kept in mind that the second target-oriented application is unlikely to provide improvement in cases where there is no technical problem in the first DBS.

4.3. Stimulation-induced Dyskinesia and Dystonia

In patients with dyskinesia, the globus pallidus internus (GPi) is the preferred stimulation target, but rarely in GPi dorsal stimulation dyskinesia may occur. Subthalamic nucleus DBS, on the other hand, is known to have a curative effect on dyskinesias due to the reduction in the use of dopaminergic therapy, even if not directly. However, STN – DBS can also cause stimulation-induced choreiform, ballistic, or dystonic movements during initial programming. Slower and longer intervals of increase in stimulation amplitude during DBS programming in these patients; in addition, proportional reduction of medical therapy may prevent the development of dyskinesia.

Preferring rapid – release levodopa monotherapy over dopamine agonists or slow-release levodopa due to its short half-life and easy titration feature provides convenience in treatment management. Activation of the dorsal contacts may be attempted to stimulate zona inserta when motor symptoms cannot be controlled due to dyskinesia. Thus, as a result of the involvement of the pallidofugal fibers extending to the GPi motor thalamus, an effect similar to STN and ventral GPi co-stimulation occurs.

4.4. Speech Disorder

Speech and voice disorders have been described as a common side effect in Parkinson's patients receiving DBS treatment, especially in STN or VIM targeted DBS cases. Speech intelligibility is impaired in the majority of patients. Speech disorder is a common adverse effect during both initial programming and long-term follow-up of STN DBS. Stimulation-induced speech disorder is thought to occur as a result of the spread of current to neighboring tissues.

High voltage stimuli, especially in the anteromedial location, may adversely affect speech intelligibility. Therefore, stimulation adjustments such as reducing the stimulation voltage, applying bipolar or interleaving stimulation, switching to low frequency (<100 Hz) stimulation can have a positive effect on speech. The relationship between speech disorder and left STN – DBS was more pronounced. When a unilateral speech disorder is detected, the stimulation settings can be adjusted accordingly.

Similarly, speech disorders can be seen in thalamus VIM DBS as a result of the spread of current to neighboring tissues, while GPi DBS rarely causes speech disorders.

4.5. Axial Symptoms

Axial symptoms such as freezing of gait, balance, posture and axial rigidity are affected by deep brain stimulation is variable. Axial symptoms that respond well to dopaminergic therapy generally also respond well to STN-DBS. In a meta-analysis study, STN-DBS evaluated postural instability and gait disturbance in the early period before surgery.

It has been shown to improve at a similar rate with medical treatment, but deterioration in axial motor features is observed in the long term. Globus Pallidus Internus DBS protects gait function better and is therefore recommended as a target for stimulation in patients with severe gait disturbance. In cases where freezing occurs only in the off state and responding to dopaminergic treatment, STN-DBS may be beneficial, whereas in cases that persist in the on state, STN-DBS will have no effect and may worsen the clinic. In these cases, it may be more appropriate to prefer GPi-DBS.

Worsening of postural instability after STN – DBS has also been reported. Recently, new DBS targets have been tried for axial symptoms. Examples of these targets are the pedunculopontine nucleus (PPN), the zona inserta, and the substantia nigra pars reticulata. In gait and balance disorders occurring in the

early period after deep brain stimulation surgery, it is necessary to exclude the presence of structural lesions, faulty electrode placement, inadequate medical treatment, and inadequate stimulation. Low-frequency stimulation or activation of the ventral contacts and stimulation of the substantia nigra pars reticulata (SNr) are the methods that can be tried to correct the gait disturbance when it is certain that there is a worsening due to stimulation. Low-frequency stimulation may improve axial symptoms in gait disturbance due to Globus pallidus DBS. Low-frequency stimulation or simultaneous stimulation of STN and SNr can be tried to correct postural instability in Parkinson's patients receiving deep brain stimulation therapy.

4.6. Ocular Disorders

Ocular abnormalities such as ocular deviation and eye opening apraxia may be seen in subthalamic nucleus DBS, mostly due to affected oculomotor nerve fibers. Ocular deviation may occur in the ipsilateral eye in the form of inward, downward, upward shift, or it may be seen as conjugated movement of both eyes. Monocular deviation suggests that the electrode is placed too medially. In this case, strategies such as reduction in stimulation parameters, active contact switching or switching to bipolar mounting can be applied. In some cases, the electrode may need to be repositioned. If conjugated eye movements are permanent, stimulation parameters adjustment is required. Eye opening apraxia low stimulation botulinum toxin application may be required in cases where the problem is not resolved by adjusting the stimulation. Ocular abnormalities have been reported more rarely in Globus Pallidus Internus DBS.

4.7. Psychiatric Problems

Symptoms such as depression, anxiety, apathy, aggressive behavior, manic episode and impulse control disorder may occur in subthalamic nucleus DBS. These symptoms, which usually occur with higher-than-normal stimulation parameters, can be improved by decreasing the density. The methods that can be applied in the treatment of these symptoms can be summarized as voltage reduction, increasing the wavelength while decreasing the voltage, increasing the wavelength while decreasing both the voltage and frequency, switching to bipolar stimulation, or activating the dorsal contact for interleaving stimulation and placing the active contacts in the dorsal position.

Management of Behavioral and Cognitive Effects of STN Stimulation

STN plays an integral role in several basal ganglia circuits associated with motor, cognitive, and emotional function and is divided into sensorimotor, associative, and limbic regions. Spread of stimulation to the ventromedial part of the nucleus (limbic region) can produce various side effects. As with motor effects, dopaminergic therapy interacts strongly with the stimulation that produces these symptoms. On the other hand, the size of the GPi results in less propagation of current from the motor to the limbic regions, which may explain the low prevalence of behavioral complications of GPi – DBS.

Hypodopaminergic behavioral syndrome may occur following STN – DBS and presents with apathy with or without depression. Presence of notable preoperative non-motor fluctuations and anxiety during the preoperative levodopa challenge test are risk factors for postoperative apathy. This syndrome may occur subacutely even with an outstanding motor outcome, or as a delayed effect months after dopaminergic drug reduction. Reinitiating dopamine agonists is the most effective method of reversing these symptoms. The use of selective serotonin reuptake inhibitors (SSRIs) may be beneficial for persistent symptoms or when severe dyskinesia limits dopaminergic therapy.

Dopamine agonist withdrawal syndrome (DAWS) patients require gradual reduction of dopamine agonist therapy which may reduce the risk. Because levodopa and dopamine agonists improve non-motor symptoms of Parkinson's disease, aggressive reduction of anti-Parkinsonian drugs should be avoided. Depression can occasionally occur without accompanying apathy. A history of depression before surgery, difficulties in adapting to life changes associated with reduced disability, and rapid postoperative withdrawal of dopamine agonists are risk factors. Antidepressant therapy, reintroduction of dopamine agonists, and psychotherapy may be helpful.

Deep brain stimulation surgical treatment is a highly effective and safe treatment option for Parkinson's disease, dystonia and essential tremor. Furthermore indications and treatment options with DBS are still expanding. However, all these diseases are chronic diseases and many surgical and device-related complications can be encountered, along with behavioral and psychiatric problems, logistics and patient.

Other problems, such as not meeting expectations, can also be seen. In order to manage this treatment effectively and with the least complications from

the very beginning of the process, it is necessary to work with a team that is competent in the aforementioned field.

It is very critical to study and select the appropriate patient. With the increase in the number of competent and sufficient centers in our country, DBS patients are indicated. While access to treatment will increase, it will also ensure that the complications that can be seen are minimized.

Abbreviations:

DAWS	*: Dopamine agonist withdrawal syndrome*
DBS	*: deep brain stimulation*
ET	*: essential tremor*
FDA	*: Food and Drug Administration*
GABA	*: Gama – aminobutyric acid*
GPi	*: globus pallidus internus*
ICD	*: Impulse control disorder*
IPG	*: implantable pulse generator*
PD	*: Parkinson's Disease*
SSRI	*: selective serotonin reuptake inhibitors*
STN	*: sub-thalamic nucleus*
QoL	*: Quality of Life*

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CHAPTER X

NEW TUNNEL TECHNIQUES IN PERIODONTOLOGY

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1. Introduction

Gingival recession is defined as the location of the marginal tissue apical to the cement-enemal junction with exposure of the root surface. It may be localized or generalized and can affect one or more tooth surfaces, with the buccal ones being most frequently affected. The root surface exposure by the gingival recession is frequently associated with dentine hypersensitivity, root caries, non-carious cervical lesions, compromised plaque control, and unaesthetic appearance. Ideally, the such characterization should be guided by a simple the classification system that is applicable and reproducible in both clinical practice and research settings. According to Miller's classification, the recession of marginal gingiva, relative to the position of a mucogingival junction and alveolar bone level, is divided into four classes as follows:

Class 1 recession that does not extend to the mucogingival junction. Class 2 recession that extends to or beyond the mucogingival junction, with no periodontal attachment loss. Class III recession that extends to or beyond the mucogingival junction, with periodontal attachment loss in the interdental area or malpositioning of the teeth. Class IV recession that extends to or beyond the mucogingival junction, with severe bone or soft-tissue loss in the interdental area and/or severe malpositioning of the teeth.

The classification by Cairo is based on the attachment loss on the buccal and proximal surfaces and has three classes:

Recession type 1 is a gingival recession with no loss of interproximal attachment. Interproximal cementoenamal junction was clinically not detectable at both mesial and distal aspects of the tooth. Recession type 2 is a gingival

recession associated with loss of interproximal attachment. The amount of interproximal attachment loss was less than or equal to the buccal attachment loss. Recession type 3 is a gingival recession associated with loss of interproximal attachment. The amount of interproximal attachment loss was higher than the buccal attachment loss.

Many techniques provide root surface closure. These; free gingival graft, bilaminar procedures, coronally positioned flap, semilunar coronally positioned flap, modified coronally positioned flap, laterally positioned flap, subepithelial connective tissue graft, connective tissue graft, guided tissue regeneration.

2. Tunnel Technique

To minimize incisions and the reflection of flaps and to provide abundant blood supply to the donor tissue, placement of the subepithelial donor connective tissue into pouches beneath papillary tunnels allows intimate contact of donor tissue with the recipient site. Positioning of the graft in the pouch and through the tunnel and coronal placement of the recessed gingival margins completely covers the donor tissue.

The technique is especially effective for the anterior maxillary area in which vestibular depth is adequate and there is suitable for gingival thickness. Since vertical releasing incision and complete papilla release are not performed with the tunnel technique, a high blood supply of the graft is achieved in the surgical area, and good aesthetic results are obtained. In addition, the tunnel technique causes traumatization and perforation of the sulcular incision.

Nart et al. (2016) Miller Class 2 and 3 achieved 83.25% root surface closure in gingival recessions in the anterior mandibular region in 15 individuals. The combination of tunnel technique and subgingival connective tissue graft should be considered treatment options to obtain root coverage in mandibular incisors with Class II and III recession defects. Ozenci et al. (2015) achieved an average of 75.7% root surface coverage in gingival recession in 10 patients with Miller Class 1, 3 mm and above with the tunnel technique. In this study comparing the coronally positioned flap and tunnel, although better results were obtained in root surface closure, the tunnel technique provided better postoperative comfort and minimal surgical trauma. This situation revealed that the tunnel technique should be modified.

3. Novel Tunnel Techniques

3.1. Modified Tunnel Technique

Initially, sulcular incisions were placed in the buccal aspect of the gingival tissues in adjacent teeth to remove sulcular epithelium and dissect the junctional epithelium. Following initial incisions, a split-thickness incision was performed so that the flap was undermined. Root planing of the exposed root surfaces was carried out until the root surfaces were hard and smooth to reduce root convexity and thus decrease the avascular surface area under the graft. The more apically located area of the root was not planned to avoid damaging the uncontaminated cementum and the connective tissue attachment. The area was irrigated with sterile saline. The partial-thickness dissection was extended, determining the intermediate papilla. The undermining incisions were extended horizontally to the mesial and distal areas to provide enough space for the subepithelial connective tissue graft. Full-thickness dissection was used to elevate the flap in the coronoapical direction. The full-thickness flap was performed in the coronoapical direction with a periosteal elevator. Care was taken to avoid perforation of the flap at the level of the mucogingival junction.

According to Tözüm et al. (2003) provided 95% root surface closure in their study. These findings suggest that subepithelial connective tissue grafting with a modified tunnel approach, in which the partial-thickness flap is converted into a full-thickness flap in the coronaoapical direction, results in adequate early healing and highly predictable root coverage in adjacent gingival recessions.

3.2. Vestibular Incision Subperiosteal Tunnel Access (VISTA)

The vestibular incision subpperiosteal tunnel access (Vista) technique provides access to the entire region with a single vertical incision and underlying alveolar bone and root dehiscence. Careful subperiosteal separation reduces the tension of the gingival margin while positioning the flap coronally. The Vista technique provides access to the underlying alveolar bone with a single vestibular incision and reduces the possibility of trauma to the gingiva. In addition, since the external incision is less, recovery is better than other techniques. In the maxillary esthetic region, the inner branches of the superior alveolar arteries run in the superior-inferior direction. Thus, the first vertically oriented incision is less likely to disrupt blood flow than horizontally positioned incisions. In addition, making the tunnel entrance from the maxillary frenum level with the first incision creates a more aesthetic result.

Gil et al. (2019) showed approximately 1 mm linear gingival thickness increase and 5.47 mm3 volume gain were obtained in 154 gingival recession areas in 21 patients. This analysis showed gingival thickness and volumetric gain achieved with Vista, in combination with different graft materials for root coverage. Rajeswari et al. (2021) achieved 93.95% root surface coverage. It is a superior alternative to Zuchelli's coronal advanced flap. Zabalegui et al. (1999) achieved an average of 91.6% root surface coverage in 21 teeth. This technique provided adequate early healing, and high root coverage results in single-stage applications of multiple retractions. Zadeh et al. (2011) Miller Class 1 and 2 provided 100% root surface coverage in two cases and were specifically recommended for the anterior region.

3.3. Modified Vestibular Incision Subperiosteal Tunnel Access

Using a 15c blade, a small vestibular incision is made through the periosteum close to the mucogingival junction in the nonkeratinized tissue. The location of this incision should be mesial to the tooth/teeth with the gingival recession defect(s). A full-thickness flap is released through the vestibular access incision using a small mucogingival elevator that is moved underneath the periosteum on top of the bone until a subperiosteal tunnel is created. In addition, the papilla adjacent to the augmented teeth is elevated from their bony surface without any incision on their surfaces. The gingival tissue, including gingival margins and papilla areas of the tooth/teeth with recession defect(s) and the adjacent teeth, has to be released entirely and movable to allow a coronal movement of at least 2 mm above the cementoenamel junction (CEJ). The dry volume stable porcine collagen matrix is cut into small pieces (approximately 5 mm x 3 mm). Using a dental plier or the small mucogingival elevator, the details can be easily placed through the access incision underneath the flap to coronally advance and augment the gingiva. Due to the relatively large volumetric dimension of the small pieces, the gingiva will have an additional thickness of patient proximately 2 to 3 mm after volume-stable porcine collagen matrix placement that will compensate for future volumetric shrinkage. In addition to the mid-buccal gingiva, volume stable porcine collagen matrix should also be placed underneath the interproximal tissue to stabilize the papilla. Anchoring 5.0 polypropylene sutures are placed approximately 2 to 3 mm below the gingival margin of each tooth to stabilize the gingiva and prevent tissue movement during the healing time. The sutures are horizontally passed through the tissue, coronally pulled, and stabilized by flowable composite on the respective teeth.

The final buccal gingival margin of each tooth should be at least 1 mm above the expected level. Volume-stable porcine collagen matrix should be entirely covered by gingiva without any exposure. Sutures are removed two weeks after surgery.

Schulze-Spate et al. (2019) case series, 100% root surfaces closure was achieved in the first and third. In the second, partial root surface closure was achieved in one tooth. Dentin sensitivity due to the gingival recession was completely healed in all three patients.

3.4. Laterally Closed Tunnel

A novel minimally invasive surgical approach, laterally closed tunnel (LCT), has been recently introduced for the management of isolated gingival recession. Subsequently, slightly beveled intrasulcular incisions were made using microsurgical blades, and a mucoperiosteal pouch (tunnel) was prepared using specially designed tunneling instruments. The pouch was then mobilized apically beyond the mucogingival line and extended mesially and distally from the recession defect by undermining the facial surface of the interdental papilla. Attaching muscles and inserting collagen fibers were separated and released from the inner aspect of the tunneled flap using microsurgical blades.

Sculen et al. (2018) achieved an average of 96.11% root surface coverage in 24 patients after treating gingival recessions in a single tooth with a laterally closed tunnel. The present results suggest that the Laterally closed tunnel is a valuable approach for the treatment of deep isolated mandibular Miller Class I, II, and III gingival recessions. Guldener et al. (2020) achieved an average of 96.6% root surface coverage in 12 patients. The present results indicate that the described treatment approach may lead to predictable root coverage of isolated mandibular Cairo Class 1 gingival recession. In another study, root surface closure results were found in 15 patients with an average of 85.1%. The present results indicate that the described treatment approach may lead to predictable root coverage of multiple mandibular and maxillary Miller Class 1 and 2.

3.5. Laterally Stretched Tunnel Flap

Intracrevicular incisions were made involving the tooth with the recession and at least one adjacent tooth to either side. A partial thickness envelope was performed with tunneling instruments involving one or two teeth adjacent to the tooth with the deep narrow recession. If the adjacent teeth present minor

recessions and/or thin biotypes, the envelope may be extended to treat these teeth with a larger connective tissue graft and a tunnel technique. A connective tissue graft obtained from the palate with the single incision technique was inserted and stabilized with simple sutures on the mesial and distal papilla. A modified single incision technique with a parallel blade handle is preferred because it provides a graft of uniform thickness (1.5 mm). The graft is inserted and held in place with sling sutures at both lateral ends of the envelope as described for the tunneling technique. Finally, the lateral edges of the recession are approximated with simple or double sutures without engaging the underlying graft to reduce the surface of the graft exposed and stabilize the wound.

In the case report of Carranza et al. (2018), they achieved 91.6% root surface closure in 6 years. The presented technique lacks vertical incisions, and an envelope approach renders a more stable wound with minimal scar formation and patient discomfort. It has shown predictable root coverage in deep narrow recession treatment. Carranza et al. (2019) achieved an average of 80% root surface coverage in 5 patients with Miller Class 2 gingival recession. The presented technique has shown predictable root coverage in deep narrow recession treatment. In addition, this technique has produced high esthetic results in medium and deep gingival recessions in the anterior region of the mandible. The laterally closed tunnel with subepithelial connective tissue graft technique may be successfully applied in the treatment of moderate and deep single gingival recessions affecting the mandibular anterior teeth when superior esthetic results are required.

3.6. Tunneled Coronally Advanced Flap

Careful attention was made to maintain the integrity of the papilla. After removing muscular insertions from the flap, the papilla were detached from the bone using tunneling mini blades and a papilla elevator. The incised anatomical papillae were de-epithelialized with a mini blade 41,42. The incised anatomical papilla were de-epithelialized using a mini blade, and the root surfaces were chemically (24% of EDTA for 2 min) and mechanically treated. The connective tissue graft was inserted into the flap from the recession area. The connective tissue graft was stabilized on the de-epithelialized anatomical papilla of the recession site with two simple spaced sutures (7/0 PGA) fixed to the periosteum from the apical of the graft, and simple spaced sutures (6/0 and 7/0 polypropylene) at the papilla level.

Barotchi et al. (2022) tunneled coronally advanced flap with connective tissue resulted in a mean root coverage of 86.5% after six months in 10 patients. The present article suggests that the tunneled coronally advanced flap with connective tissue graft is a suitable technique for treating isolated Miller Class 1 gingival recession. The newly introduced technique may have the potential to enhance flap blood supply and graft vascularization and improve clinical, esthetic, and patient-reported outcomes of Miller Class 2 gingival recession with deficient papilla. Barootchi et al. in two cases, all areas healed uneventfully after the treatments. Complete root coverage was achieved and maintained during follow-up observations between 6 and 18 months. Patients reported minimal discomfort and reduced dentin hypersensitivity in the augmented areas.

3.7. Modified Coronally Advanced Flap

Intrasulcular incision was conducted along the recession margins up to the adjacent papilla using a micro single-edge scalpel blade. Next, vertical releasing incisions were made starting laterally at the base of the papilla, 2 mm apical from the sulcus of adjacent teeth, up to and beyond the mucogingival junction. Then, a mucoperiosteal full-thickness flap was raised using tunnel elevators, extending it by a few millimeters apical to the base of the recession. Attaching muscles and inserting collagen fibers were separated and released from the inner aspect of the tunneled flap using microsurgical blades and Gracey curettes. Finally, to achieve complete mobilization of the flap, the interdental papillae were gently undermined using the specially designed tunneling knife. After tunnel preparation, a palatal subepitelial connective tissue graft of a thickness of 1 to 1.5 mm was harvested using the single incision technique. Subepitelial connective tissue graft was pulled in the tunnel using single or mattress sutures and fixed at the inner aspect of the tunnel flap. Subsequently, the graft was immobilized at the cementoenamel junction or slightly below using a 6-0 sling suture to obtain complete stability. Finally, the tunnel flap was advanced coronally to completely cover the graft and the recession using sling sutures.

Molnar et al. (2013) achieved 71% root surface coverage in 42 gingival recessions, Miller Class 1 and 2. Sculean et al. (2014) looked at Class 1 and 2 gingival recessions of 3 mm and above in 16 patients and achieved 96.25% root surface coverage at the end of year. The present results indicate that the described treatment approach may lead to predictable root coverage of isolated mandibular Miller Class I and II gingival recessions. Sculean et al. (2016), in another study of 54 gingival recessions classified as Class 1, 2, and 3. 96% root

surface coverage was achieved. The present findings indicate that the proposed treatment concept results in predictable coverage of multiple adjacent maxillary Miller Class I, II, and III gingival recessions. Finally, Lanzrein et al. (2020) 85.1% root surface closure was achieved in Class 1 and 2 multiple gingival recessions in the maxilla and mandible in 15 patients with Class 1 and 2 gingival recessions of 2 mm and above.

3.8. Tunneling Coronally Advanced Flap

Intrasulcular incision was conducted along the recession margins up to the adjacent papilla using a micro single-edge scalpel blade. Vertical releasing incisions were made starting laterally at the base of the papilla, 2 mm apical from the sulcus of adjacent teeth, up to and beyond the mucogingival junction. Using tunnel elevators, a mucoperiosteal full-thickness flap was raised, extending it by a few millimeters apical to the base of the recession. Finally, the flap was mobilized using a no. 15 blade, conducting deep supra periosteal and superficial incisions for muscle dissection. The graft was sutured over the root with a resorbable 6.0 polyglycolic suture (PGA). Then the mucoperiosteal flap was advanced over the cementoenamel junction (CEJ) and fixed with 6.0 polypropylene sling sutures.

Chiantella et al. in his study, 3-6 gingival recessions were closed in depth and width in five patients. This case report proposes a microsurgical tunnel coronal advanced flap with the inclusion of adjacent papilla for treating single Miller Class 1 and 2 gingival recessions with connective autografts or xenografts.

3.9. Coronally Advanced Tunnel Flap

The gingival tissue was undermined and extended into the mucosal tissues around the buccal surface of each involved tooth, and individual pouch preparations were connected. The tunneling preparation was achieved with blades or with the use of tunneling knives. Next, a full-thickness preparation of the papillary region was prepared using periosteal elevators to allow the flap to be advanced coronally. The harvested subepithelial connective tissue from palate was then positioned and trimmed to the required size with a sharp 15c surgical blade, and a support suture was performed to guide the subepitelial connective tissue graft into the recipient site. The graft was gently pushed into the tunnel pouch with a packing instrument and by pulling the support suture. In case of multiple recession defects in adjacent teeth, the securing needle was

passed passively underneath the tunnel created between the adjacent recessions. The suture was passed from the mesial aspect of the tunnel and pushed gently to the distal direction with a periosteal elevator so the graft could slide underneath the tunnel. The graft was placed coronally into the cementoenamel junction and the entire gingivopapillary complex was moved coronally using 5-0 polyglactin sutures in the interdental spaces fixed to the palate gingiva such that the sutures captured.

Bhatavadekar et al. (2019) the modified coronally positioned flap and the coronally advanced tunnel flap were compared in 36 patients in the adjacent gingival recession. No significant difference was found in root surface closure. Both surgical techniques were similarly efficient in treating multiple recessions in the short term and in maintaining the stability of therapy in the medium and long term.

3.10. Combination of Laterally Closed Tunnel and Coronally Advanced Tunnel

Intrasulcular incisions were placed mesially, distally, and facially at the involved teeth using microsurgical blades. Using specially designed tunneling instruments, a mucoperiosteal tunnel was prepared beyond the level of the mucogingival junction leaving the interdental papilla intact and extended apically and laterally from the recessions. Attaching muscles and inserting collagen fibers were separated and released from the inner aspect of the tunnel using the microsurgical blades and the Gracey curettes. The tension-free prepared tunnel was finally checked by placing a periodontal probe under the papilla. Following tunnel preparation, a palatal subepitelial connective tissue graft with a thickness of 1.0 to 1.5 mm was harvested using the single incision technique. In contrast, the closure of the palatal donor site was immediately performed using 5-0 modified mattress sutures. The subepitelial connective tissue graft was then drawn into the single recession area and fixed mesially and distally at the inner aspect of the tunnel using either simple or mattress sutures. Finally, the margins of the tunnel were either approximated together over the graft and sutured with interrupted sutures or positioned coronally with sling sutures to accomplish tension-free complete or partial coverage of the graft and the root surfaces.

Sculean et al. (2021) combined the laterally closed tunnel and coronally advanced tunnel in 40 mandibular multiple gingival recessions in 11 patients. Primarily this region is suitable for withdrawals. The results of the present case

series suggest that the laterally closed tunnel and coronally advanced tunnel is a valuable technique for the treatment of mandibular Miller Class 1 gingival recession.

The tunnel technique is still valid in its original form and continues to be applied. Although the tunnel technique has started to be used in multiple retractions in the maxilla and mandible, it can now be used in single retractions in its modified form. Other techniques developed based on the tunnel technique gave as much or sometimes better results as the tunnel technique.

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CHAPTER XI

NEW APPROACHES IN GLAUCOMA SURGERY AND MINIMALLY INVASIVE GLAUCOMA SURGERY

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1. Glaucoma Surgery

Glaucoma is the second most common cause of preventable blindness in the world. Its prevalence among people over 60 years of age is 2%. The total number of patients with glaucoma worldwide is predicted to increase to 111.8 million in 2040. Glaucoma, according to its latest definition, is a kind of optic neuropathy with retinal nerve fiber loss and compatible visual field defects and the most important and modifiable risk factor is increased intraocular pressure (IOP).

Mechanisms that cause glaucomatous optic neuropathy, retinal ganglion cell degeneration, and retinal nerve fiber loss were explained by vascular and mechanical theories. The mechanical theory suggests that increased IOP leads to the degeneration of optic nerve axons at the level of the lamina cribrosa and induced apoptosis causes permanent damage. On the other hand, vascular theory explains the ganglion cell and axonal damage in the glaucomatous pathogenesis as being due to deprived vasoregulation and perfusion, metabolic end-product accumulation and eventual apoptosis.

The main target of both medical and surgical treatment for glaucoma is to reduce the intraocular pressure to IOP where axonal damage is at the level of damage caused by normal aging. Agents used in medical therapy decrease IOP either by decreasing aqueous humor production or increasing aqueous humor (AH) drainage.

Despite the advances in medical therapy, medical treatment alone is still not sufficient for all patients, and surgical and laser procedures are needed to control glaucoma. Moreover, medical treatment brings a huge economic burden to the health system, causes serious ocular and systemic side effects, and reduces the quality of life of patients. Eventually, it causes disruptions in treatment and difficulties in glaucoma control. Surgical treatment of glaucoma is needed in some patients and it's still the most powerful weapon against the silent thief of the visual field.

There are conventional approaches and innovations in the surgical treatment of glaucoma. Conventional glaucoma surgeries can be examined under the following headings:

1. Trabeculectomy
2. Glaucoma drainage tubes (seton surgery)
3. Cyclodestructive operations

1.1. Trabeculectomy

Trabeculectomy was used as the first option for surgical intervention in thousands of glaucoma patients since it was first described in 1968 and is accepted as the gold standard for the surgical treatment of glaucoma. Trabeculectomy is performed by opening a conjunctival and tenon flap, partial thickness scleral flap and sclerostomy, through which AH drains into subconjunctival space and forms a filtering bleb, and also iridectomy to prevent pupillary block obstruction of the sclerostomy.

Covering the sclerostomy with the sutured scleral flap and conjunctiva-tenon flap provides relatively controlled filtration which is determined by the tightness of the sutures and intact conjunctival covering. It is a proven treatment to control IOP and diurnal fluctuations in IOP. However, serious visual complications of this surgical method, which may lead to possible eye loss, led surgeons to search for safer and more effective modifications in the application of surgery or other surgical options.

Postoperative complications of trabeculectomy include shallow anterior chamber, bleb leaks, lens-corneal contact, hypotony, hypotonic maculopathy, choroidal detachment, suprachoroidal hemorrhage, bleb-related infections, and endophthalmitis.

1.1.1. New Approaches in Trabeculectomy Surgery

1.1.1.1. Trabeculectomy with Antimetabolite

Excessive wound healing response and subconjunctival fibrosis after trabeculectomy surgery cause bleb failure and decreased AH drainage. Subconjunctival fibrosis, which causes bleb failure after surgery, is targeted with modifications such as the application of antifibrotic agents such as mitomycin C (MMC) and 5-fluorouracil (5-FU) to the subconjunctival area during surgery. Studies showed that the combination of trabeculectomy with antimetabolites increases surgical success in patients with a high risk of bleb failure and long-term survival rate. Recently the use of Ologen collagen matrix implant was introduced and found to control fibrous tissue formation; thus, decreasing the chances of failure.

1.1.1.2. Laser Suturolysis

Control of hypotonia is very important in the postoperative management of trabeculectomy. Measures taken to avoid postoperative hypotonia during surgery include tight suturing of the scleral flap, tight closure of the tenon and conjunctiva, and avoidance of buttonhole formation. In the absence of excessive filtration in the early postoperative period, controlled IOP reduction is achieved by opening the scleral tight suture and increasing filtration. The application of laser suturolysis with an argon laser ensures controlled filtration in the postoperative period.

1.1.1.3. Removable Suture Techniques

Various removable suture techniques were developed to provide controlled filtration in the postoperative period. Removal of sutures to increase postoperative filtration can be successfully used to provide early postoperative controlled filtration.

1.2. Glaucoma Drainage Tubes (Seton Surgery)

Conventionally, glaucoma drainage tube (GDT) surgery is considered in cases with low success rate for trabeculectomy like scarred conjunctiva, neovascular glaucoma, and uveitic glaucoma with excessive healing response, or glaucoma drainage tube surgery may be considered when previous trabeculectomy fails. Glaucoma drainage tubes basically consist of two parts;

the silicon tubes which shunt AH from the anterior chamber to a plate with changing shape, and surface area providing drainage to the subconjunctival space. Commercially available and most commonly used tubes are Ahmed (New World Medical, Inc., Rancho Cucamonga, CA), Baerveldt (Advanced Medical Optics, Inc., Santa Ana, CA), Krupin (Eagle Vision, Inc., Memphis, TN), and Molteno (Molteno Ophthalmic Ltd., Dunedin, New Zealand). The surface areas of the plate vary between 96-500 mm2 in different types of tubes and models. Valved tubes have a valve mechanism that prevents the development of hypotonia due to excessive drainage of postoperative aqueous humor. Ahmed and Krupin valves are examples of valved tubes. In valveless tubes, tube suturing ensures postoperative hypotonia control and the plan is to remove sutures placed in the tube after the surgery. Among the innovations made in GDT surgery in recent studies are antimetabolite applications and tube tip placement in the sulcus. GDT and trabeculectomy were compared in randomized prospective studies and success rates were found to be similar.

1.3. Cyclodestructive Procedures

Cyclodestructive procedures are considered in glaucoma control when other surgical methods are not applicable or successful. It is generally applied for eyes with end-stage glaucoma and low visual potential. It is based on the principle of destruction of the ciliary processes producing AH with a laser probe or cryoprobe. Collateral tissue damage of the ciliary processes causes complications that are difficult to predict. Intraocular inflammation, hypotonia, and phthisis bulbi are among these complications. Due to the low predictability of cryotherapy complications, it is no longer applied for the most part.

1.3.1. Transscleral Cyclophotocoagulation

Transscleral cyclophotocoagulation utilizes a continuous wave 810 nm diode laser system and delivers laser energy to ciliary body processes transsclerally. Absorption of laser energy by melanin containing ciliary pigment epithelium leads to coagulative necrosis and decreases in production of AH. Meanwhile, simultaneous collateral tissue damage leads to complications like intraocular inflammation and prolonged hypotony. Because of anatomical variations in eye anatomy and changing pigment concentrations in an eye, transscleral application leads to variable and unpredictable results.

1.3.2. Endoscopic Cyclophotocoagulation

Endoscopic cyclophotocoagulatin uses a 175 W xenon light, helium-neon targeting beam, a probe with video-camera and ophthalmic continuous-wave pulsed 810 nm diode laser which allows laser applications to the ciliary processes with direct visualization. Thus, more selective and targeted treatments with less unpredictable postoperative hypotonia are possible. The main disadvantage of this approach is the intraocular application, which carries the risk of cataract formation, infection, and other possible intraocular complications.

1.3.3. Micropulse Transscleral Cyclophotocoagulation

The micropulse transscleral cyclophotocoagulation system provides transscleral fractionated energy delivery in repetitive on and off cycles. "On cycles" permit effective energy to be delivered to ciliary body epithelium and "off cycles" ensure cooling between pulses; thus, reducing collateral tissue damage and reducing complications like inflammation and hypotony. The micropulse transscleral cyclophotocoagulation provides effective IOP lowering, and a decreased rate of complications compared to traditional transscleral cyclophotocoagulation with the continuous wave.

1.3.4. High-intensity focused ultrasound (HIFU)

The high-intensity focused ultrasound (HIFU) is a kind of contact ultrasound cyclo- plasty procedure. HIFU provides selective destruction of the ciliary body tissue via highly focused ultrasound beams. EyeOP1 device (Eye Tech Care, Rillieux-la-Pape, France) is a second-generation HIFU device and it has received the CE mark in May 2011 and Chinese FDA approval in October 2017. The HIFU device has a coupling cone made up of polymer containing 6 active piezoelectric elements at the base. The piezoelectric transducers produce ultrasound beams, which converge to create a controlled thermal ablation of the distal part of the ciliary body processes. Recent studies showed that in addition to ciliary body necrosis, HIFU also enhances the uveoscleral outflow, providing a dual mechanism of IOP reduction. Recent studies reported 30-38% IOP reduction and 30-90% success rates with HIFU and minimal side effects.

2. Microincisional Glaucoma Surgery (MIGS)

Microincisional glaucoma surgery is a procedure that aims to provide faster postoperative recovery period and less complications, as well as effective IOP-

lowering effects of glaucoma surgeries. According to Saheb and Ahmed, the term MIGS refers to a group of surgical procedures which share five preferable qualities: an ab interno approach through a clear corneal incision which spares the conjunctiva of incision, minimally traumatic procedure to the target tissue, IOP lowering efficacy that justifies the approach, high safety profile avoiding serious complications compared to other glaucoma surgeries, and rapid recovery with minimal impact on the patient's quality of life.

In a workshop of the American Glaucoma Society and the US Food and Drug Administration (FDA) held in February 2014, the term "minimally invasive glaucoma surgery" was featured with the implantation of a surgical device intended to lower IOP via an outflow mechanism with either an ab interno or ab externo approach, associated with very little or no scleral dissection. In most of these surgeries, the basic aim is to bypass the juxtacanalicular trabeculum, which creates the highest resistance to AH outflow.

In recent years, MIGS surgeries have gained popularity alongside conventional glaucoma surgeries. The complications of these surgeries are low, postoperative patient recovery is faster, patients require less hospitalization, surgery can be combined with cataract surgery, and the area of application is increasing. However, the unpredictability of IOP-lowering potential and IOP fluctuations in the postoperative period creates drawbacks in advanced glaucoma cases. Moreover, the long-term results of these surgeries are not fully known, and research continues in this area. Examples of existing MIGS surgeries and main characteristics of them are shown in Table 1.

2.1. Trabectome

A trabectome ((NeoMedix, Tustin, California, USA) is a device that provides infusion, aspiration and electrocautery with the help of a pedal, which enables the removal of a thin strip from the trabecular mesh and Schlemm canal under gonioscopic imaging and with an ab interno approach in open-angle eyes. (Figure 1) It was approved for clinical use by the FDA in April 2004. It is one of the first surgeries evaluated in the MIGS class, with no scleral dissection, low complication rates, and rapid wound healing. It can be combined with cataract surgery. In recent studies, it was reported that trabectome surgery provides 30-40% IOP reduction and the 5-year surgical success rate is between 60-80%.

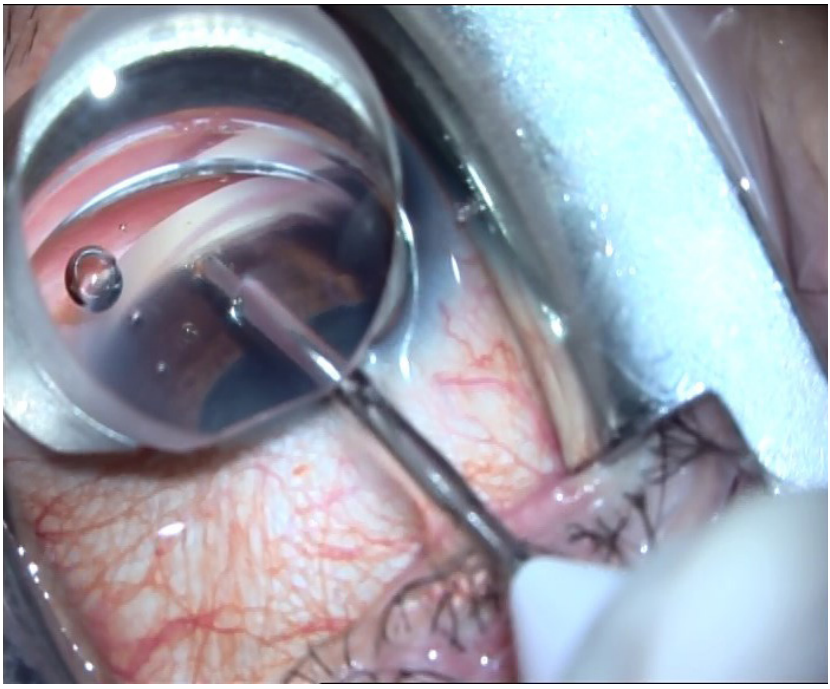

Figure 1. Trabectome surgery. Gonioscopic view of trabecular ablation by Trabectome. (from the archive of Dr. Yıldıray Yıldırım)

2.2. Xen Gel Implantation

The XEN gel stent (Allergan plc, Dublin, Ireland) is a 6 mm long, 45 µm lumen diameter stent produced from porcine collagen cross-linked with glutaraldehyde. It received CE certification in 2011 and US FDA approval in 2016. Stent implantation can be combined with cataract surgery or it can be applied alone. The Xen gel stent is placed through a small, transparent corneal incision with an inserter with one end at an angle and the other end in the subconjunctival area. This application is also among MIGS procedures because the integrity of the conjunctiva is preserved. Aqueous drainage is provided to the subconjunctival area through the tube and a bleb is formed. This procedure can be performed in eyes with healthy conjunctiva. MM-C is usually applied in the procedure to ensure the bleb remains functional. Studies reported a 20-48% reduction in IOP and different surgical success rates in the range of 40-88% with Xen gel implantation. However, serious complications such as hypotonia, choroidal detachment, tube malposition, exposure, endophthalmitis, and bleb complications were reported after Xen-gel implantation.

2.3. I-stent and I-stent Inject

I-stent and i-stent inject (Glaukos Corporation, Laguna Hills, CA, USA) are 1st and 2nd generation, respectively, heparin-coated trabecular by-pass devices made of non-ferromagnetic titanium. I-stent inject is 360 µm in length with a diameter of 230 µm. It is marketed as a preloaded syringe. I-stent inject is the smallest implant implanted in the human body. They are often combined with cataract surgery. With gonioscopic imaging, they are implanted ab interno in the trabecular meshwork with the tip in Schlemm's canal and bypass resistance created by the juxtacanalicular network in the aqueous outflow path. The combination of this microimplant with cataract surgery was shown to provide an effective reduction in IOP.

2.4. Hydrus Microstent

The Hydrus micro-stent (Ivantis Inc., Irvine, CA, USA) is a flexible and biocompatible implant made of an 8 mm long nickel-titanium alloy, also called the 'intracanalicular scaffold', which is implanted inside the Sclemm canal. It is implanted ab internally through a clear corneal incision into the nasal quadrant with a preloaded syringe. Once placed in the canal of Schlemm, the tube is opened in the canal, and the trabecular meshwork is bypassed and it increases the drainage of AH through the collector canals. It is often combined with cataract surgery. At the end of one year, at least a 20% IOP reduction was reported with Hydrus.

2.5. Cypass

Cypass (Transcend Medical, Menlo Park, CA, USA) is a 6.35 mm long, 300-mm lumen implant in a fenestrated polyamide structure. Endothelial failure was reported with this implant, which is implanted ab internally between the ciliary body and the sclera and drains the AH into the suprachoroidal area, and the implant was withdrawn from the market in 2018 although it received FDA approval in 2016.

2.6. I-stent Supra

The I-stent supra is a 3rd generation implant made of polyethersulfone and colored titanium with a length of 4 mm and a lumen diameter of 1.6-1.7 mm. It is implanted with a clear corneal incision over the ciliary body with the tip angled into the suprachoroidal space. It was CE certified in 2010, but there is not

enough information about its clinical effectiveness as it has not been released to the market yet.

2.7. Gonioscopy-Assisted Transluminal Trabeculotomy (GATT)

This method, which was described by Grover et al. in 2014, is a 360-degree trabeculotomy by advancing a prolene suture through the Schlemm canal 360 degrees through the ab interno goniotomy incision using gonioscopic imaging and pulling the 2 suture ends.(Figures 2 and 3) This surgery can be listed among MIGS surgeries in terms of being ab interno and not involving conjunctival and scleral incisions. In the 2-year results of GATT surgery, 40% IOP reduction and surgical success rates of over 80% were reported. Long-term results of GATT surgery are expected.

2.8. Kahook Dual Blade (KDB)

The KDB (New World Medical, CA) is a type of ophthalmic blade with 2 parallel sharp tips designed for the excision of a strip approximately 230 microns wide from the trabeculum and Schlemm canal. It received FDA approval in 2015. Trabeculotomy with KDB increases the outflow of AH and lowers IOP. It can be combined with cataract surgery. An 11-34% decrease in IOP was reported with KDB.

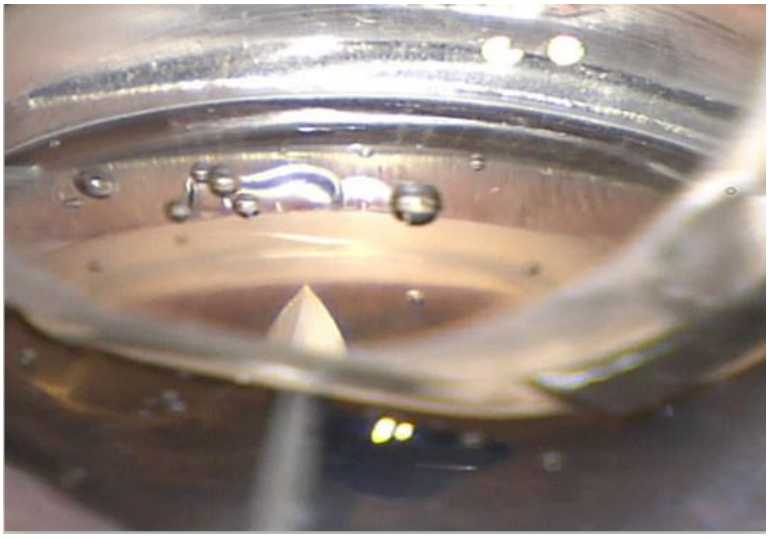

Figure 2. Gonioscopic view of GATT surgery, creation of goniotomy is seen. (from the archive of Dr. Serhat Imamoglu).

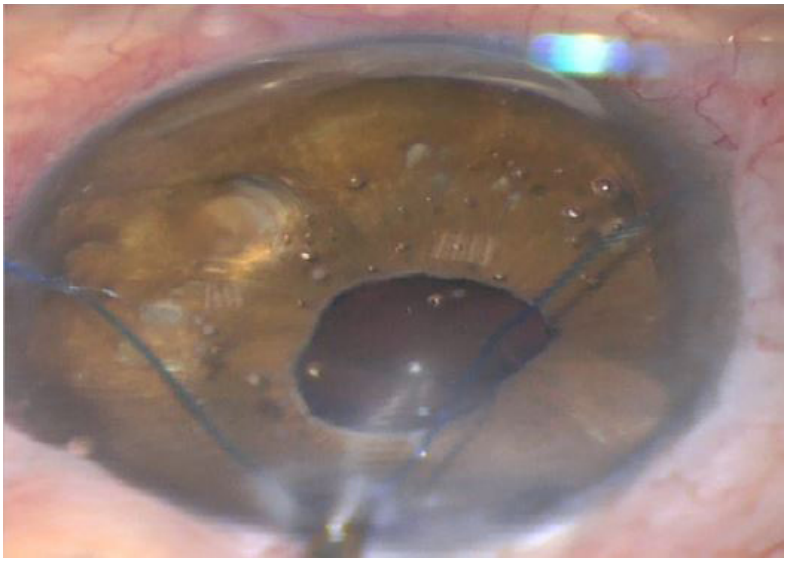

Figure 3. Pulling the proximal part of the suture which has passed through Schlemm canal to complete 360 degrees trabeculotomy. (from the archive of Dr. Serhat Imamoglu).

2.9. PRESERFLO MicroShunt

The PRESERFLO MicroShunt is an 8.5 mm long, 1.1 mm wide tube with an inner diameter of 70 µm and an outer diameter of 350 µm. It is a synthetic polymer of poly (styrene-block-isobutylene-block-styrene) (SIBS). It is implanted ab-externo and drains AH from the anterior chamber into the subconjunctival space. It has 2 fins 4.5 mm behind the tip, which is placed in the anterior chamber, and ensures stability of its position. Although it involves conjunctival and tenon dissection, it is listed in MIGS because it does not include scleral dissection and propulsion time is relatively shorter. It can be applied with MM-C. The PRESERFLO MicroShunt was approved and released in 2019. However, there is no FDA approval. There is not enough information about its effectiveness.

Table 1.

MIGS	Outflow pathway & surgical approach	Possible Complications	Diameters
Trabectome	Trabecular Ab-interno	Hemorrhage	-
Xen gel implant	Subconjunctival Ab-externo	Hypotony Choroidal detachment	6 mm
I-stent and I-stent inject	Suprachoroidal Ab-interno	Hemorrhage	0.3x1 mm/ 360x230 μm
Hydrus microstent	Trabecular Ab-interno	Hemorrhage Angle synechia	8 mm
Cypass	Trabecular Ab-interno	Hypotony Endothelial deficiency	6.35 mm
I-stent supra	Suprachoroidal Ab-interno	Under investigation	4 mm
Gonioscopy-assisted transluminal trabeculotomy	Trabecular Ab-interno	Hemorrhage	-
Kahook Dual Blade	Trabecular Ab-interno	Hemorrhage	-
PRESERFLO Microshunt	Subconjunctival Ab-externo	Hypotony	8.5 mm

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CHAPTER XII

ROBOTIC SURGERY IN OPHTHALMOLOGY

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The word "robot" was first used by Czech writer Karel Capek in 1920 in relation to R.U.R.-Rossum's universal robots. The word means "work" in the Czech language. Robots were originally intended to be used as mechanical workers to do the jobs that no one wanted to do. However, in the last 10 years, developments in computer technology and their combination with artificial intelligence have allowed robots to take on roles that help people, support human skills, eliminate margins of error, and even exceed human skills.

Similar to its integration in all areas of life, robot technology has been used in many surgical fields of medicine. However, for more delicate surgeries, such as eye surgery, cardiovascular surgery, and neurosurgery, which require 150–200 μ mobility and are affected by human factors, interest in the use of robots in these areas has increased due to robots' superhuman abilities. Intraocular surgeries must be performed with extreme accuracy and precision in a small workspace. It is difficult to accurately target a specific anatomical site or to keep the surgical instrument stationary for long periods of time. Human physiological hand tremors can significantly impact the outcomes of surgery, especially in macular surgery involving thicknesses of 2.5 μm. The tremor amplitude projected onto the tip of the collet by a successful surgeon is 24-22-20 micrometers in the x-y-z axes, and the tremor area is a surface of 182 micrometers. The recurrence rate of physiological tremors is between 8–12 Hertz. These tremors can cause serious problems in macular surgery and intravenous procedures.

One of the human limitations in microsurgery is also force perception. Experimental studies have shown that a force of only 7 mN can cause a retinal tear in the rabbit retina, while surgeons can feel less than 20% of events performed at forces of this magnitude.

The eye has a small volume for the surgical field and needs precise maneuvers. There are human limitations and challenges in eye surgery. In ophthalmology, surgical robots have the potential to advance treatments, reduce complication rates, and treat incurable conditions. Robots are being integrated into ophthalmological surgical procedures because they offer high sensitivity, motion control, anti-tremor, advanced visualization, and distance sensing improvements.

The stereo-taxical micromanipulator for ocular surgery, one of the first prototypes for robotic surgery in ophthalmology, was developed by Guerrouad and Vidal in France in 1989. In the early 1990s, Hunter et al. built a system called the "remote tele-operated system," which is a preliminary model of today's robotic telesurgery system. A similar system was made by the NASA laboratory in the USA. In 1998, Constable et al. in Austria succeeded in penetrating the central retinal artery in the animal eye with remote commands. In the same year, a 30 micrometer microcannula was successfully entered into the 70-micrometer vessel lumen with a robotic application at the University of Tokyo. During this period, Riviere et al. developed a micromanipulator called Micron with anti-tremor. U-Xuan Tan et al. and Gonenc et al. also contributed to robotic surgery with the anti-tremor micromanipulators they developed in the same period.

There are four different robotic applications in ophthalmic surgery based on the approach to using these instruments.

1. Systems Supporting The Surgeon/Robot-Assisted Tools

In these systems/tools, the surgical instrument itself was modified to be a miniature robotic system. The robotic tool offers tremor cancelation, depth locking, and other features, while the surgeon controls this tool to perform a hands-on surgical procedure.

An example of this type of tool is the MICRON (Fig. 1). It was developed in 2010 in collaboration with the Robotics Institute at Carnegie Mellon University and Johns Hopkins University. The Micron consists of a motion-sensing module mounted at the back end of the steady-hand instrument handle that sensed translational and rotational motions in six degrees of freedom (DOF). It uses a dynamic sinusoidal model to cancel erroneous motion by predicting frequency, amplitude, and phase of surgeon tremor. The Micron increased the success of retinal intravenous injection from 29% to 63% in experimental models. In 2015, the Gough–Steward platform that constrained the remote center of motion near the tool tip was added, resulting in a 90% reduction in hand tremors and less than

25 μ in error in hand circle tracking. The success rate will be further increased with the new force-sensing needle. However, to date, related studies have been conducted only on artificial or animal eye models.

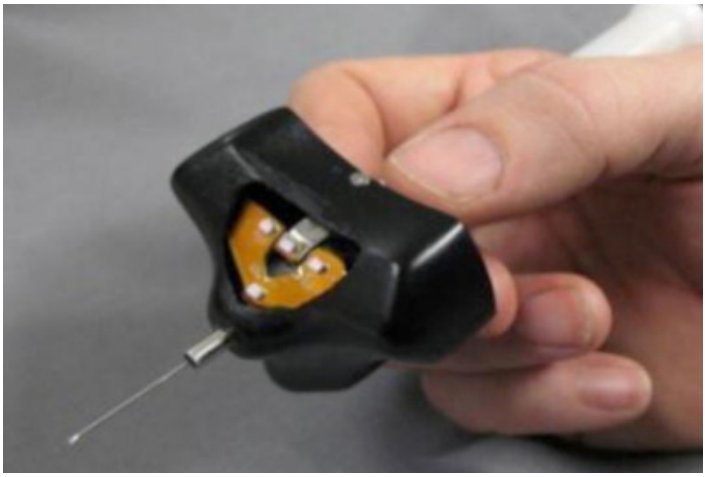

Figure 1. The MICRON. A hand-held robotic manipulator.

MacLachlan RA, Becker BC, Tabarés JC, et al. Micron: an actively stabilized handheld tool for microsurgery. IEEE Trans Robot. 2011;28:195–212.

2. Surgeon Collaborative System

In this system, power sensors are integrated into the instruments used by the surgeon, and these sensors participate simultaneously with the surgeon in robotic center manipulations, with feedback stimuli coming from the power sensors. This robotic system takes joint initiative with the surgeon in terms of tremor control, the amount of force applied to the tip of the collet, or the position of the collet. Visual feedback is obtained via the microscope and/or optic coherence tomography (OCT).

2.1. Catholic University of Leuven System

Catholic University of Leuven System was presented in 2014 by the Micro- and Precision Engineering Group at the Catholic University of Leuven (Fig. 2). This system reduces hand tremor and facilitates the ability to maintain a stable position for extended periods, thus offering the surgeon greater stability and precision. The system consists of a parallel arm mechanism with a mechanical remote center of motion (RCM) controlled by a spherical mechanism.

This system has obtained very successful results in intravenous applications that require stabilization. In an in vivo study in pigs, the needle tip was fixed in the intravenous position for more than 3 minutes in 15 of 18 eyes. Successful retinal vein cannulation in in vivo pig eyes was then followed by a four-case human study. The human study involved an injection of Ocriplasmin into the target retinal vessel for 10 minutes. These successful results demonstrated the technical feasibility of robot technology. The robotic system is currently under development for clinical applications by MYNUTIA, a subsidiary of the university.

Figure 2. The intraocular robotic system of the Catholic University of Leuven. Gijbels A, Smits J, Schoevaerdts L, et al. In-human robot-assisted retinal vein cannulation, a world first. Ann Biomed Eng. 2018;46:1676-1685.

2.2. The Steady-Hand Eye Robot (SHER)

SHER is another collaborative robotic system developed by Johns Hopkins Hospital (Fig. 3). SHER includes both a significantly improved manipulator and an integrated micro force sensing tool. In this system, the surgeon and the robot control the operator-initiated movements together. In addition to filtering the surgeon's hand tremor, SHER prevents excessive force on the instrument tip with real-time feedback from the force-measuring sensors to the device. With this force scaling feature, it aims to improve the challenges of precision retinal surgery.

However, since its flat and rigid structure can only approach the target from one direction, it is restricted by certain limitations. However, the snake-like distal tip (Integrated Robotic Intraocular Snake; IRIS) integrated into the SHER may increase the ease of manipulation.

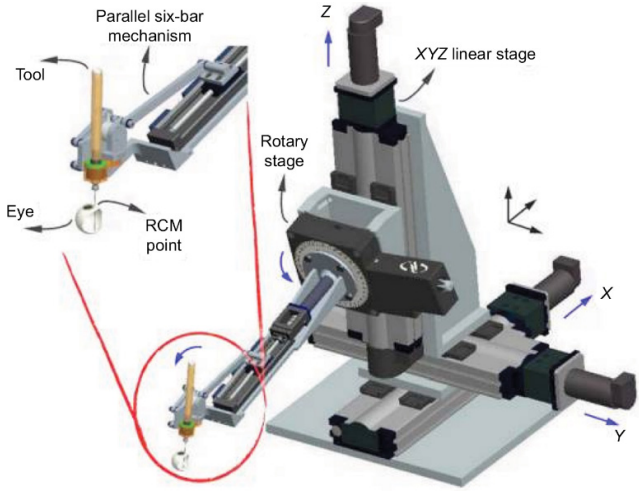

Figure 3. The Steady-Hand Eye Robot (SHER) (RCM, Remote center of motion). Roizenblatt M, Edwards TL, Gehlbach PL. Robot-assisted vitreoretinal surgery: current perspectives. Robot Surg. 2018;5:1-11.

3. Remote-Controlled Robotic Surgery

In this type of system, the surgeon controls a robotic system using joysticks. The surgeon and patient may not be in the same room. The surgeon uses an optical microscope or a digital head-up display for visual feedback. The surgical instrument is in the robot's hand. The surgeon can then direct the robot by moving the joystick in their hand. The instrument in the robot's hand is capable of haptic feedback, jitter filtering, and motion scaling. Examples of these remote-controlled robot systems include the Da Vinci Surgical System, RAM!S, Preceyes Surgery System, and the intraocular robotic interventional surgery system (IRISS).

3.1. Da Vinci Surgical System

The Da Vinci Surgical System (Intuitive Surgical, California USA), one of the robotic surgery systems, has been used successfully in many fields of surgery since 2000. In ophthalmology, it has been successfully applied in anterior and posterior segment surgeries in animal experiments. It has a stereoscopic image, an anti-tremor feature, the ability to enlarge the image, and a stabilization system that limits the surgeon's movements and enables delicate work. It has been used successfully in laceration repair, intraocular foreign body removal, penetrating keratoplasty, anterior capsulotomy, and pterygium surgery.

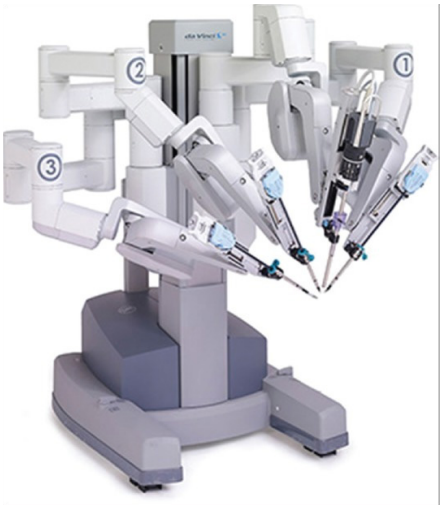

Figure 4. Da Vinci Surgical System. Pandey SK, Sharma V. Robotics and ophthalmology: are we there yet? Indian J Ophthalmol. 2019;67:988-94.

However, it also has limitations. The robotic arms are not as intuitive as wrist movements, the endoscope view is worse than the microscope view, and high stress is applied to the sclerotomy area. However, the developed Hexapod Surgical System provides an RCM dedicated to intraocular robotic surgery with a high level of precision and dexterity.

3.2. RAM!S

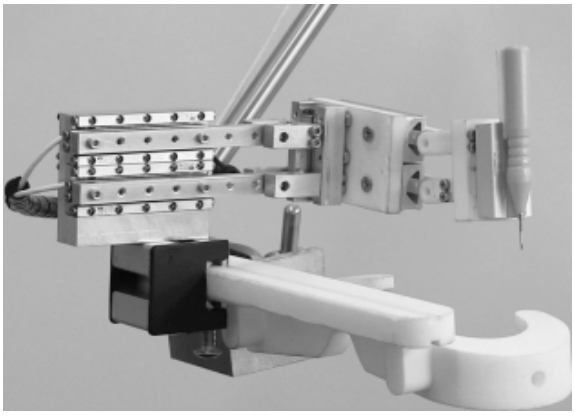

Figure 5. The RAM!S System. Nasseri MA, Eder M, Eberts D, et al. Kinematics and dynamics analysis of a hybrid parallel-serial micromanipulator designed for biomedical applications. IEEE/ASME International Conference on Advanced Intelligent Mechatronics. 2013;293–9.

The RAM!S (Fig. 5) is an articulated system developed at the Technical University of Munich in 2013 and connected to a piezoelectric motor. The mechanism consists of two joints coupled in parallel, one prismatic joint, and one optional revolute joint to collectively enable six DOF of tool motion. It is designed to be fixed on the patient's head.

In the researchers' recent studies, the performance of the device's software-constrained RCM was evaluated using a tissue model and ex vivo pig eyes, and the RCM was shown to operate with an accuracy of 1 mm. It has seen great success in subretinal depth guidance with a 5 μ tool tip position accuracy, power feedback controller, and OCT feedback.

3.3. The Preceyes Surgical System

The Preceyes Surgical System (Fig. 6) was developed by the Eindhoven University of Technology in the Netherlands and was later further developed by Preceyes BV, a spin-off company at the university. It consists of a joystick held by the surgeon and a robotic system that controls the surgical instrument and performs physical manipulation of the intraocular tissue. The surgeon uses a standard surgical microscope for visual feedback. The design of the robotic system is based on a parallelogram connection that is common to many surgical robotic systems. This design offers a mechanical RCM and improved tool tip position accuracy. An adjustable counterweight keeps the system in a fixed position to enhance safety in the case of system failure or power loss. It has been successfully used to treat venous occlusions in pig eyes with a 10 μm tool tip positional resolution.

A clinical trial in 2018 compared this system to conventional surgery. It was used to remove a flap of the retinal membrane under general anesthesia in 12 patients with macular holes. Also, subretinal injections were successfully completed in three cases. The robotically assisted procedures resulted in less iatrogenic retinal trauma and microbleeds. There were no system failures or technical glitches. Although robot-assisted surgery takes longer than unassisted surgery, the increased sensitivity of the robotic system and fewer surgical complications offer a bright future for the inclusion of robots in the field of intraocular surgery. Thus, Preceyes recently received CE marking status.

3.4. Intraocular Robotic Interventional Surgical System (IRISS)

IRISS (Fig. 7) was developed by the Mechatronics and Control Laboratory and the Stein Eye Institute at the University of California, Los Angeles. First

introduced in 2013, this system aims to perform the most sensitive surgeries, including anterior and posterior segment surgeries, through combinations of augmented reality teleoperation and full automation. Its double-arm structure allows for the simultaneous use of two instruments in the eye. In addition, it has a quick tool change feature that allows any tool to be mounted and switched outside the eye in milliseconds. The stereo camera integrated into the digital microscope transmits the three-dimensional image to the surgeon via an overhead monitor.

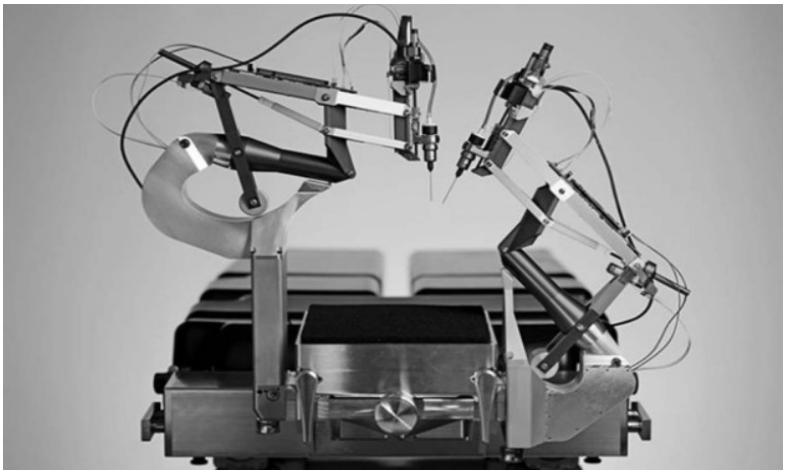

Figure 6. The Preceyes Surgical System. Gerber MJ, Pettenkofer M, Hubschman JP. Advanced robotic surgical systems in ophthalmology. Eye (Lond). 2020;34:1554-62.

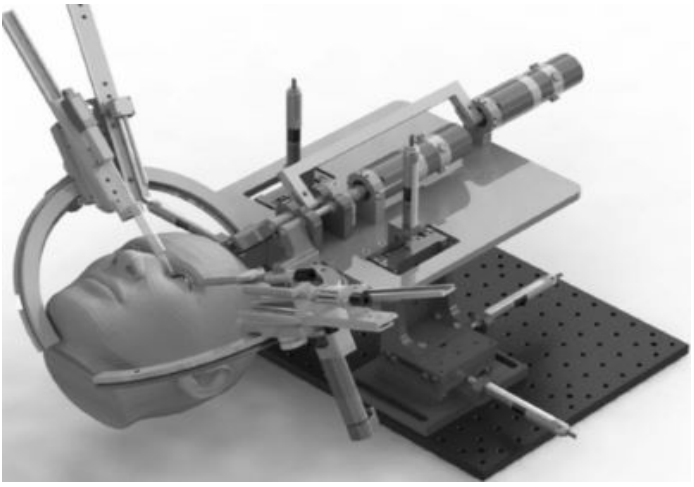

Figure 7. Intraocular robotic interventional surgical system (IRISS). Gerber MJ, Pettenkofer M, Hubschman JP. Advanced robotic surgical systems in ophthalmology. Eye (Lond). 2020;34:1554-62.

The IRISS has allowed surgeons to successfully perform capsulorhexis, viscoelastic injection, hydrodissection, lens aspiration, vitrectomy, and retinal vein cannulation with teleoperation. However, an OCT system was integrated into the IRISS to avoid potential complications due to surgeons' physiological limitations and lack of sensing ability. This feedback system was used for automated cataract surgery.

The robotic system automatically aligns itself to the eye, and structures within the anterior segment are identified using preoperative OCT volume scan models. Thus, a surgical plan that enhances safety and increases efficiency and productivity can be developed. While the lens removal step is fully automated, intraoperative OCT scans at the instrument tip are displayed to the surgeon in real time, allowing the surgeon to intervene manually. This robotic system, integrated with OCT, has been successfully applied to ex vivo pig eyes. It is the first robotic system to successfully perform all steps of cataract surgery.

In the future, the IRISS system aims to assist in the performance of surgery with an augmented reality cockpit integrated with OCT feedback and auditory and tactile sensory feedback (Fig. 8).

4. Magnetically guided robots

Magnetically guided systems use an extraocular magnetic field to control robotic microcapsules inside the eye (Fig. 9). Kummer et al. used the OctoMag magnetic system to manage an intraocular microrobot with high maneuverability. This system provides a high level of intraocular dexterity and maneuverability without physical attachment to the extraocular space. However, very complex magnetic field generators occupy a large area around the patient's head. These systems can be used in the management of retinal vein cannulation and drug-releasing microcapsules.

Charreyron et al. used steerable magnetic-tipped catheters to deliver subretinal gene therapy injections. The group developed semi-autonomous control that automatically aligns the instrument's magnetic field to keep the instrument tip perpendicular to the retinal surface at a surgeon-specified target area. The user determines when the instrument tip is optimally placed for injection while monitoring instrument manipulation through the microscope. Magnetic micromanipulators retain the advantages of intraocular dexterity and offer a potential safety advantage over traditional rigid surgical instruments due to their limited stiffness and limitations of achievable forces. Currently, this semi-autonomous system is under extensive research to make it fully autonomous.

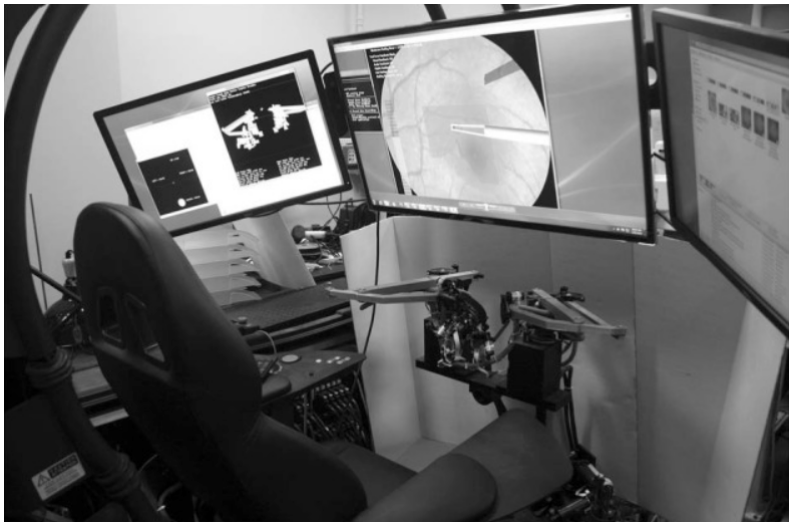

Figure 8. IRISS Cockpit protype. Gerber MJ, Pettenkofer M, Hubschman JP. Advanced robotic surgical systems in ophthalmology. Eye (Lond). 2020;34:1554-62.

5. Force Sensor

Forces applied to the retina during surgery are beneath the surgeon's ability to detect. Therefore, the development of force-sensing devices and their integration into microsurgical instruments provides many benefits, including improved safety, instrument response to forces, and the potential to create a record of forces applied during surgery. For this purpose, a series of force-sensing devices have been developed at Johns Hopkins University with varying DOF and increased robustness. The forces applied to the instrument at the point of contact with the eyewall affect the forces measured at the instrument tip. While the RCM concept in robotics assumes only three rotational DOFs at the scleral entry point and one translational DOF along the instrument axis, all lateral translations are prohibited by mechanical constraints at the entry point. Each DOF has a significant effect on the motion accuracy of the instrument.

Gonenc et al. designed micro forceps that sense three DOF forces. They then developed a family of forceps that could measure force directly from the tool tip inside the eye, with force sensors placed at the tip of the tool. Thus, both the forces detected by force sensing at the tip of the surgical instrument and the forces detected at the point of entry of the instrument into the sclera provide important intraoperative information. With this technology, iatrogenic retinal injuries that may occur due to excessive but imperceptible forces applied during

surgery will be prevented in the future. A new forceps also is in development that automatically releases tissue when force limits are met.

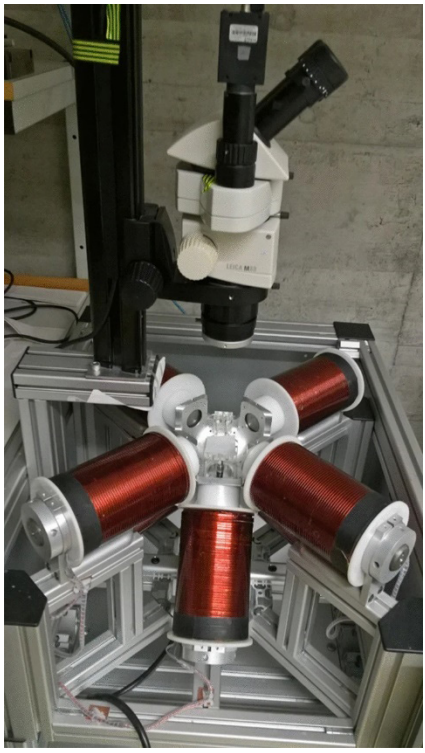

Figure 9. Magnetically guided robots, OctoMag. Ahronovich EZ, Simaan N, Joos KM. A review of robotic and OCT-aided systems for vitreoretinal surgery. Adv Ther. 2021;38:2114-29.

6. Optical Coherence Tomography (OCT)

OCT is a diagnostic and surgical planning ophthalmic tool that can develop cross-sectional images of tissue using light reflection. After advances in OCT technology, swept-source OCT has improved the applicability of retinal multimodal digital images and improved diagnostic accuracy in the clinic. Integration of OCT with the operating microscope provides enhanced feedback on the position of the surgical instrument.

Lack of sense of proximity is an important factor that contributes to surgical risk and may reduce the likelihood of achieving surgical goals. Recently, intraoperative real-time images were provided by inserting the OCT probe into the 23-gauge and 25-gauge trocars or forceps. Thus, OCT has been used as

a distance sensor for intraoperative vehicle control and as a real-time image orientation method.

7. Current Studies And The Future Of Robotic Surgery In Ophthalmology

In the practice of ophthalmology, robotic systems offer hope for the future, as they enable high precision and the possibility of impossible surgeries.

Successfully integrated laser technologies (femtosecond lasers) in cataract surgery have been applied with high precision and confidence to reduce intraoperative complication rates. However, human skills are still required to clean the lens material. Shin et al. successfully completed ex vivo semiautomatic extraction of lens fragments using a surgical robot and semantic segmentation of OCT images with deep learning. Chen et al. performed OCT image-guided lens extraction semi-automatically, where posterior capsular rupture was not observed in any of the patients. Gerber et al. successfully performed ex vivo posterior capsule polishing with OCT image guidance. In the future, robotic systems may combine high-resolution intraoperative OCT imaging with robotic maneuvers and full automation to allow the complete cleaning of lens material and particles that cause posterior capsule opacification while reducing posterior capsule perforation complications.

Most of the work on robotic surgery has focused on the vitreoretinal area due to its sensitive work environment. Robotic applications can replace human performance in retinal applications due to their high sensitivity and accuracy. Successful ex vivo results have been reported in robotic surgical membrane peeling, vein cannulation, and automated laser applications. The robotic system also allows the administration of anticoagulants in retinal vein occlusions in both animal models and human patients, with long-term stability in the vein. Another potential application is in gene and stem cell therapy in severe retinal disorders. Although these systems have not yet gained widespread validity, they offer hope for the future.

Success in robotic surgery is closely related to imaging systems. Currently, many studies are underway to improve and develop imaging systems. In particular, intraocular OCT devices facilitate the surgical procedure by providing real-time images of epiretinal or internal retinal membrane peeling. The incorporation of OCT into microsurgical instruments also results in a significant reduction in surgeon's hand tremors. OCT added to 25-gauge force-sensing smart microsurgical forceps has shown promise in vitreoretinal surgeries.

OCT-guided robotic systems have shown promise in corneal surgery in ex vivo studies on automatic keratoplasty sutures and deep anterior lamellar keratoplasty. Bourcier et al. successfully performed extraocular muscle surgery using a robotic system in an experimental eye. Furthermore, robot-assisted CyberKnife has been successfully applied in the treatment of iris melanoma and choroidal metastasis. In addition, CyberKnife stereotactic robotic radiotherapy showed promise in primary or secondary orbital lesions.

Studies continue to show that the robotic system can also be used in the education of trainees and that surgical steps can be learned more quickly. These data can also be added to a deep learning module, making future robotic systems more seamless. Thus, robotic systems may be partially or fully automated in the near future and complete surgical tasks independently of the surgeon. Furthermore, artificial intelligence-guided systems may even have the ability to make surgical decisions in the distant future.

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CHAPTER XIII

MIX-AND-MATCH INTRA–OCULAR LENS IMPLANTATION WITH THE USE OF EDOF & TRIFOCAL LENSES IN CATARACT SURGERY

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1. Introduction

The correction of presbyopia is the "holy grail" in refractive surgery. Individuals spend more of their activities of daily living on near or intermediate tasks such as smart phones and computers. This has led to a greater desire to achieve the full range of vision without spectacles or contact lenses.

Advances in cataract surgery and intra – ocular lens *(IOL)* technology, and the increase in patient expectations, have led to improvements in IOL designs. With the new designs, uninterrupted clear vision at close, intermediate and long distances, high contrast sensitivity and correction of astigmatism are aimed. Presbyopic IOLs allow for the potential of spectacle and contact lens independence. These implants can be used at the time of a refractive lens exchange or cataract surgery.

Multifocal intraocular lenses met the need for near and far vision without glasses, but were insufficient at intermediate distances. Trifocal intraocular lenses have been developed to meet the need for intermediate vision. However, problems such as halo and glare and decreased contrast sensitivity in trifocal intraocular lenses affect the quality of vision negatively. To eliminate this, diffractive lenses with enhanced depth of focus *(EDOF)* have been developed. EDOF technology, on the other hand, aims to compensate the loss of contrast sensitivity with trifocal lenses by increasing the amount of light passing to the retina and increasing the contrast sensitivity, thereby ameliorating the visual

quality *(VA)*. However, near vision is significantly impaired with EDOF lenses compared to trifocals.

In this case, the ophtalmatologist came up with an innovative surgical approach via implanting the EDOF lens to the dominant eye and trifocal lens to the other as a ‘’mix and match surgery’’ in order to leverage the upsides of both lenses.

2. The Anatomical Structure & Physiology of Lens

The lens is located in front of the patellar fossa formed by the anterior hyaloid membrane behind the iris. It has a biconvex structure and the convexity of its posterior surface is greater than that of the anterior. It is attached to the ciliary body by zonules from the equatorial region. The equatorial diameter of the lens is approximately 6 mm at birth. By adulthood, it reaches about 9 mm. The anterior posterior length is approximately 3 mm at birth and 5 mm at adulthood. The average refractive power of the lens is 19.7 D. The back side of the lens may cause 0.5 D astigmatism, but this situation is balanced by the 0.5 D compliant physiological astigmatism of the cornea.

The lens is covered with an elastic capsule of collagen structure. It is mainly composed of type IV collagen and glycoproteins. The thickness of the capsule is greatest in the pre-equatorial region where the zonules adhere, and the least in the equatorial and anterior posterior poles. Under the capsule is a single row of cuboidal epithelial cells. Of these epithelial cells located at the equator, they actively divide to form lens fibrils. Other epithelial cells exchange substances with aqueous humor and secrete capsule material.

The lens tissue is composed of a high percentage of protein. It consists of approximately 2/3 of its weight of water, 1/3 of proteins and a small amount of other substances *(amino acids, electrolytes, lipids)*. The rays under 300 nanometers *(nm)* wavelength are absorbed by the cornea. Wavelengths between 300 – 400nm are absorbed by the lens. The lens transmits 95% of the incident light. The remainder is mostly reflected by the cell membranes in the lens.

Energy production in the lens is mostly achieved by anaerobic respiration of glucose passing through the aqueous fluid. Aerobic respiration is limited to the lens epithelium. A small part of glucose metabolism takes place via sorbitol pathway. Due to the low diffusion rate of sorbitol into the aqueous fluid, it is known that water withdrawal due to its accumulation in the lens has a role in the formation of diabetic cataracts.

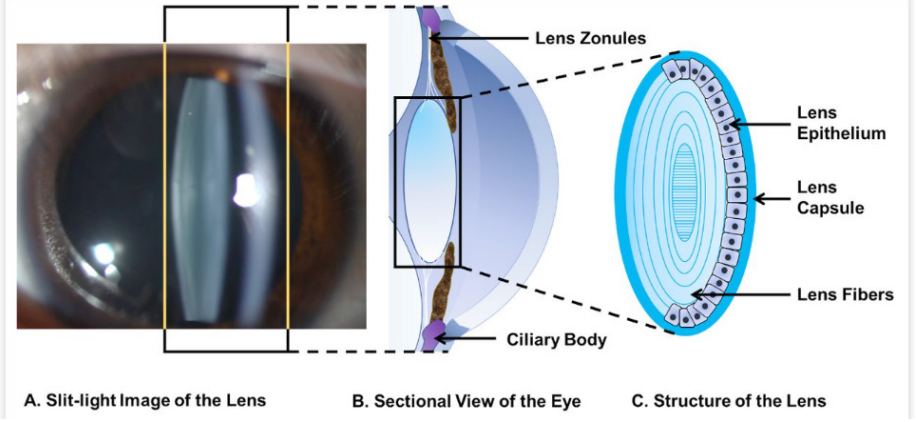


Figure 1: Lens and its physiological function in vision

The amount of water in the lens is mainly balanced by the sodium pump. Disruption of this balance is one of the causes of cataract formation. In addition, the increase in calcium concentration in the lens can have a cytotoxic effect on the lens cells. The proteins in the lens are divided into soluble crystalline and insoluble albuminoid. With advancing age, the amount of albuminoid protein increases while the crystalline protein content in the lens decreases. This situation is thought to play a role in senility-related cataract.

3. Cataract

Cataract is one of the leading causes of preventable blindness all over the world. Cataract is a localized or diffuse increase in opacity in the lens. In advanced ages, epithelial cells become flattened and their proliferation rate decreases. As a result, epithelial density decreases. The lens capsule also thickens over time. These changes reduce the transparency of the lens.

Although many factors are counted in its etiology, the mechanism of formation has not been fully elucidated. Risk factors include advanced age, genetics, smoking and alcohol consumption, increased body/mass index, ultraviolet – b *(UV – B)* exposure, radiation, drug use *(steroid, phenothiazine, allopurinol)*.

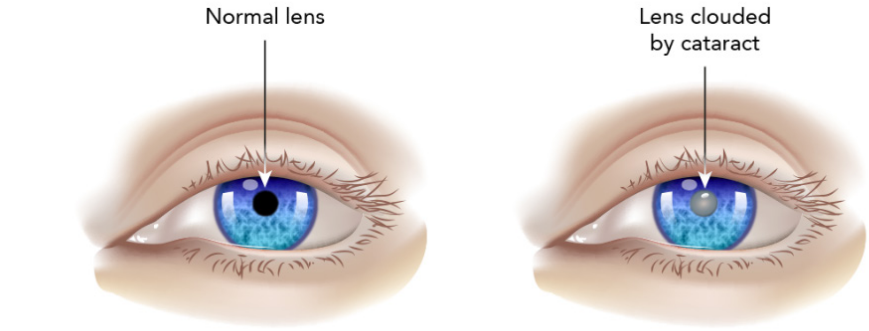


Figure 2: The normal eye and cataract

There are generally 2 different methods for the classification of cataracts. In the first method it is divided into *cortical, nuclear, anterior and posterior subcapsular, mixed and other cataracts* according to their anatomical localization. According to its etiology, it is grouped as *congenital, developmental or juvenile, senile, pathological, traumatic, complicated and secondary* cataracts.

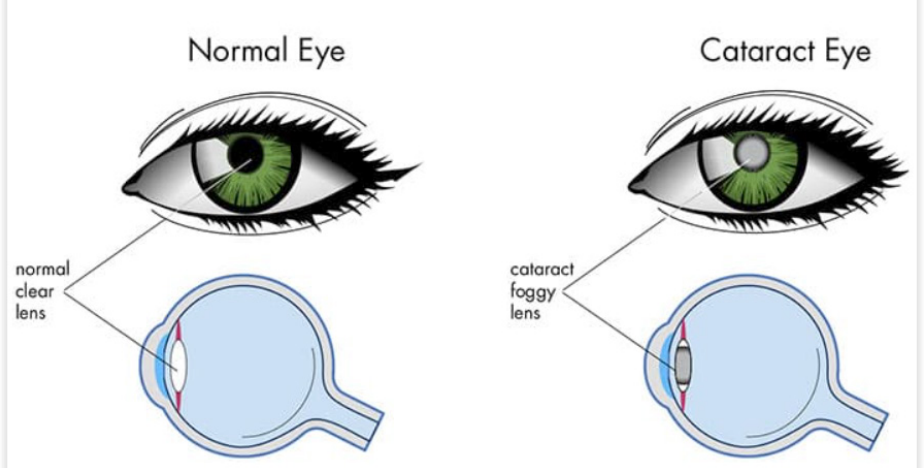


Figure 3: Change in lens due to cataract

Senile cataracts are the most common type of cataract in the elderly. As age progresses, weight gain and thickening are observed in the lens. Chemical changes in the structural proteins of the lens lead to the accumulation of proteins. This reduces the transparency of the lens and causes light scattering. The lens first turns yellow and then turns brown.

Senile cataracts are morphologically examined in 3 groups:

3.1. Nuclear Cataract

It is a type of cataract that develops as a result of age-related color change due to the accumulation of urochrome pigment in the lens nucleus, hardening of the lens and sclerotic changes in the lens. These changes usually begin in the fetal nucleus and occur over the years. It is usually seen bilaterally and asymmetrically. Evaluation of the developing nuclear cataract is done with a slit lamp.

As the lens density and refractive index increase, false myopia develops. Although this myopia can be corrected with refraction correction in the early period, a decrease in visual acuity is observed in the future.

3.2. Cortical Cataract

According to the morphological classification of senile cataracts, it is the most common type of cataract. The thickness of the lens cortex is 2 mm in total on the anterior and posterior surfaces in adulthood. The lens cortex is in fluid exchange with the aqueous humor. The cortex is more active and less compact in terms of vital activities than the nucleus. For this reason, electrolyte imbalance begins primarily in this layer. The onset of protein degradation and denaturation in the lens triggers this.

The first sign of cortical opacity is the formation of vacuoles in the lens and destruction of the lens fibers. In the following periods, wedge-shaped opacities occur that can be observed biomicroscopically. They are best observed with retroillumination light. Cortical opacity usually begins to form in the inferonasal quadrant. Although the exact cause is unknown, this supports the relationship between cataract and UV rays exposure. Until these concentrations extend to the optic axis, patients have good visual acuity.

3.3. Posterior Subcapsular Cataract

Posterior subcapsular cataract is typically located centrally just in front of the posterior capsule. Since it is located in the optic axis from the beginning period, it gives symptoms in the early period. The visual acuity of the patient, who previously had complaints of light scattering and glare, also decreases in the following period. Generally, the patient complains of an increase in complaints while reading in the light. It has been shown that posterior subcapsular cataract may be associated with radiation exposure, long-term systemic steroid use, and diabetes.

The etiology of posterior subcapsular cataract is between the posterior capsule and the cortex, the death of the lens cells. As a result debris and progression of capsule epithelial cells are thought to occur. These powdery structures become plaques in the future and adhere tightly to the posterior capsule. This makes it difficult to clear the plaque during cataract surgery and increases the risk of posterior capsule rupture.

Cataracts are usually uniform in the beginning. In the future, an increase in opacity occurs in the layers and the cataract becomes mixed. As a result of the progression of the cataract, mature cataract occurs. At this stage, fundus reflex cannot be obtained in biomicroscopic examination. If the cortex layer of the lens, whose water balance is disturbed, absorbs excess water and swells, it is called intumescent cataract cortex in later stages. The brown nucleus displaces inferiorly. This state of the lens is called morgagnian cataract. Finally, a hypermature cataract occurs as a result of the loss of some of this fluid. At this stage, the lens is white and shiny. Pigments can be seen in the anterior chamber. These pigments can trigger macrophage activation and trigger phacolytic glaucoma.

Effects of cataract on visual function can be elaborated as: decrease in visual acuity, decrease in contrast sensitivity, monocular diplopia, color perception impairment, visual field loss and glare. Cataracts can be diagnosed by biomicroscopic examination in patients with these symptoms.

There are several classification systems for grading the intensity of cataracts. *"Lens Opacities Classification System III* (*LOCSIII)*" is the most widely used system today. In this system, cortical and posterior subcapsular opacification is divided into 5 groups and nuclear sclerosis is divided into 6 groups. In addition, cataract diagnosis, grading and follow-up with Kowa early cataract detector and Scheimpflug photo biomicroscope devices. can be done.

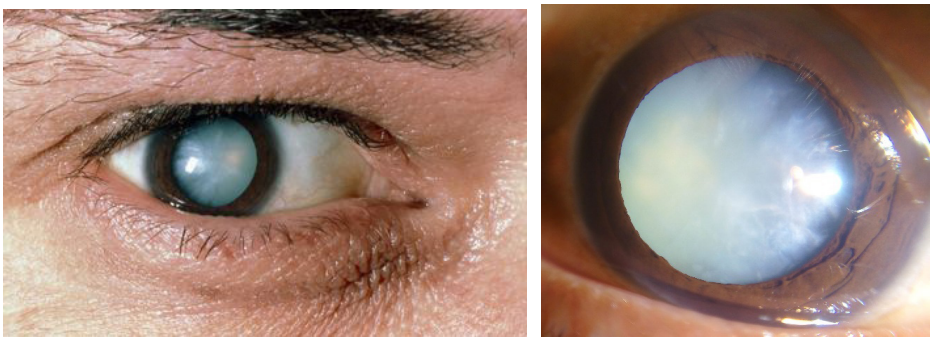


Figure 4: Examination of a cataract patient

4. Intra – Ocular Lenses *(IOLs)*

Silicone lenses were first used in 1984. They had the ability to fold easily. Since the refractive index is low, their thickness increases at high 15 diopters and they become more difficult to fold. There are single and 3-piece models. Decentralization problem was tried to be overcome by using PMMA haptic.

Silicon is sensitive to the Neodymium-Yttrium-Aluminium-Garnet *(Nd – YAG)* laser, so care must be taken when opening the posterior capsule opacities. The back surfaces of silicone lenses may become opaque when in contact with intravitreal gases. They also interact with intravitreal silicone. This may make it difficult for the surgeon to see the retina during pars plana vitrectomy. Second generation silicon lenses were made of pure silicone material caused less problems.

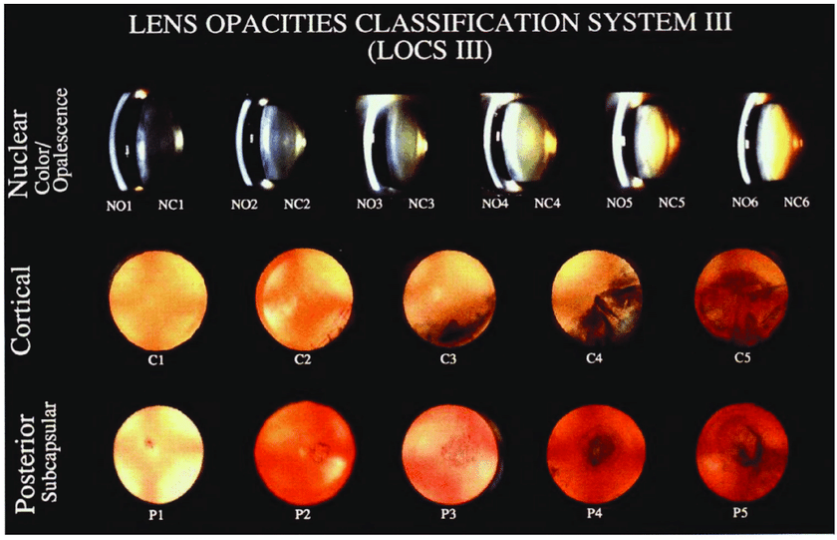


Figure 5: Lens Opacities Classification System III (LOCSIII)

Acrylic intraocular lenses produce less posterior capsule opacity. Nd – YAG is more resistant to laser and is thin due to its high refractive index. It also has high optical quality like PMMA. They are safer against capsule traumas as they open more slowly than silicone material. For this reason, it is the most preferred lens material in our day. Hydrophobic acrylic lenses are prone to surface trauma, therefore it is recommended to be placed with the injector system. With the use of high posterior capsule adhesion and sharp edges, the risk of posterior capsule opacity is low. Hydrophilic acrylic lenses are more resistant to trauma, but have a greater risk of developing posterior capsule opacity than hydrophobic acrylics.

4.1. Toric Intraocular Lenses

Approximately 20% of patients with cataracts have cornea greater than 1.5D hence astigmatism is present. There are various methods applied to the cornea to correct this, but these are interventions with low predictability and limited. Therefore, the production of toric intraocular lenses was needed. The first toric intraocular lens was designed by *Shimizu et al. in 1992.*

4.2. Multifocal Intraocular Lenses (MFIOL)

Multifocal intraocular lenses have been developed for the purpose of seeing the near, middle and far distances clearly independently of glasses. Unlike accommodative intraocular lenses, they function independently of the ciliary body. It is tried to provide clear vision at all distances by using the diffraction and refraction feature of the light.

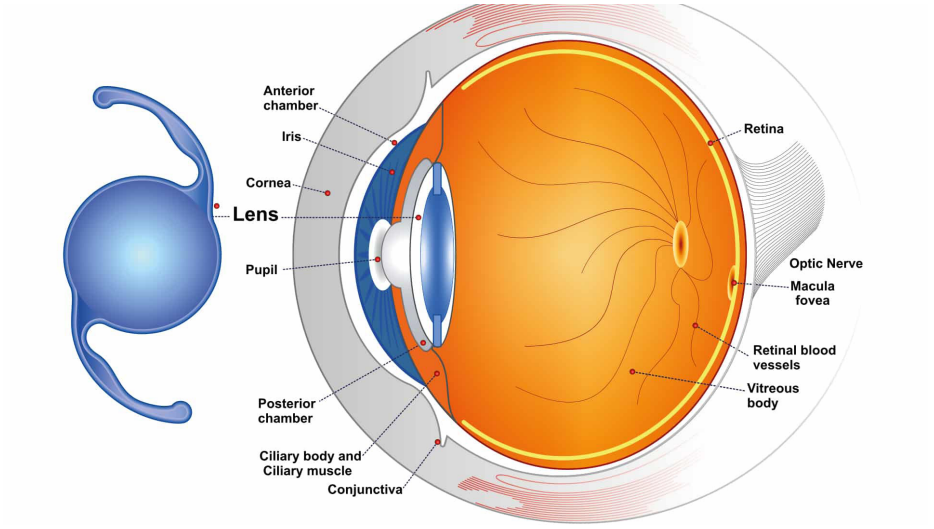


Figure 6: Multi-focal intra-ocular lenses

4.3. Refractive Multifocal Intraocular Lenses

Refraction is the refractive index of light that changes direction as it passes between different media. Refractive multifocal IOLs *(MIOLs)* have nested concentric refractive rings. In the power plant, a circle for long distance is designed as a ring for close distance, and then again as a long distance ring. Aspheric versions are designed to reduce spherical aberrations in these lenses.

Aspheric zones distribute this multifocality evenly over the lens surface. However, pupil size and ambient lighting continue to affect image quality. Pupil size determines the distribution of light to the refractive rings. When looking close, the narrowing pupil directs the light to the near focused ring; pupil growing as you look away directs the majority to the far focus. Because refractive MFIOLs divide the light into focal points, the transitions are harsh and often produce halo and glow effects.

4.4. Diffractive Multifocal Intraocular Lenses

Diffraction means the refraction or bending of light. When light rays pass through a narrower range than their wavelength, the wavelength and direction of the light change. Diffractive MFIOLs are designed to form multiple narrow gaps like this. As a result of the diffraction of the light beam coming into the eye, rays with different wavelengths and directions are formed, which pass to the retina. The ones in the same phase of these rays merge and those in opposite phase cancel each other out, while producing a higher energy beam.

This phenomenon is called interference. These positive and negative interferences increase the modulation transfer function *(MTF)*. Side-by-side prisms are used to create the slits in this model. If the curvature is preserved and the thickness is reduced as a result of compression of the monofocal lenses, the objects formed are called fresnel lenses.

By adding microscopic prisms to the lenses, we obtain kinoform lenses. Kinoform lenses form the basis of diffractive MFIOLs. The kinoform lens system is applied to all diffractive rings. The prism closest to the center is called the first-order prism. As you move away from the center, the second and third rows are created. While the height of the prism determines the sharing ratio of the incident light rays, the width of the base determines the focal distance. The narrower the base width, the shorter the focal distance. If the base widths are the same, the addition power of the first row is half as much as the second row of prisms. In lenses with this design, approximately 41% of the incident light is used for near and 41% for far, while 18% is lost. This distribution is pupil-independent, unlike refractive lenses. In diffractive bifocal intraocular lens designs, the power of the first row prisms is set to +3.5 D on average. If the widths are assumed to be the same, the power of the second row prism corresponds to +7D. These prisms create 2 foci for 10 cm and 30 cm and a good bifocality for near vision occurs.

4.5. Trifocal Intraocular Lenses

Diffractive bifocal intraocular lenses provide good near and far vision. Although they provide sharpness and contrast sensitivity, they are not sufficient at intermediate distance. For this purpose, trifocal intraocular lenses were formed by roughly the combination of two bifocal diffractive lenses. The power of the first order prism in these lenses was determined as +1.75 D on average. In this design, 20% of the beam leaving the +1.75D prism is approximately half is used in +3.50D prism and beam loss is reduced. Thus, the first prism creates the intermediate distance at approximately 60 cm, and a close distance focus is created at 30 cm with the second row of prisms.

4.6. Intraocular Lenses with Enhanced Depth Of Focus (EDOF)

EDOF technology has been developed to get rid of the halo and glare effect in trifocal lenses, to increase contrast sensitivity, and to provide uninterrupted clear vision. In these lenses, an expanded depth of focus is created instead of creating different focuses by sharing or scattering the light. It achieves this with the "*echelette"* design on its diffractive surface. The prisms in this design create a seamless image. In 2016, Tecnis Symphony received "*Food and Drug Administration (FDA)*" approval for the first time with its EDOF lens. This IOL is bi-convex. It has an aspherical surface designed with wavefront technology. The back has an achromatic, diffractive, *"echelette"* design. With this design, it transmits almost all of the light to the retina and reduces chromatic aberrations.

5. Phacoemulsification Technique

The phacoemulsification technique was discovered and developed by *Charles D. Kelman in the 1960s.* This technique was developed with the thought of allowing the *ECCE technique* to be performed through a smaller corneal incision. Although it was not popular at first due to its complications, it became widespread again in the 1970s with the introduction of the irrigation-aspiration technique. With the production of viscoelastics consisting of various substances in the 1980s, modern phacoemulsification surgery has become the most preferred method.

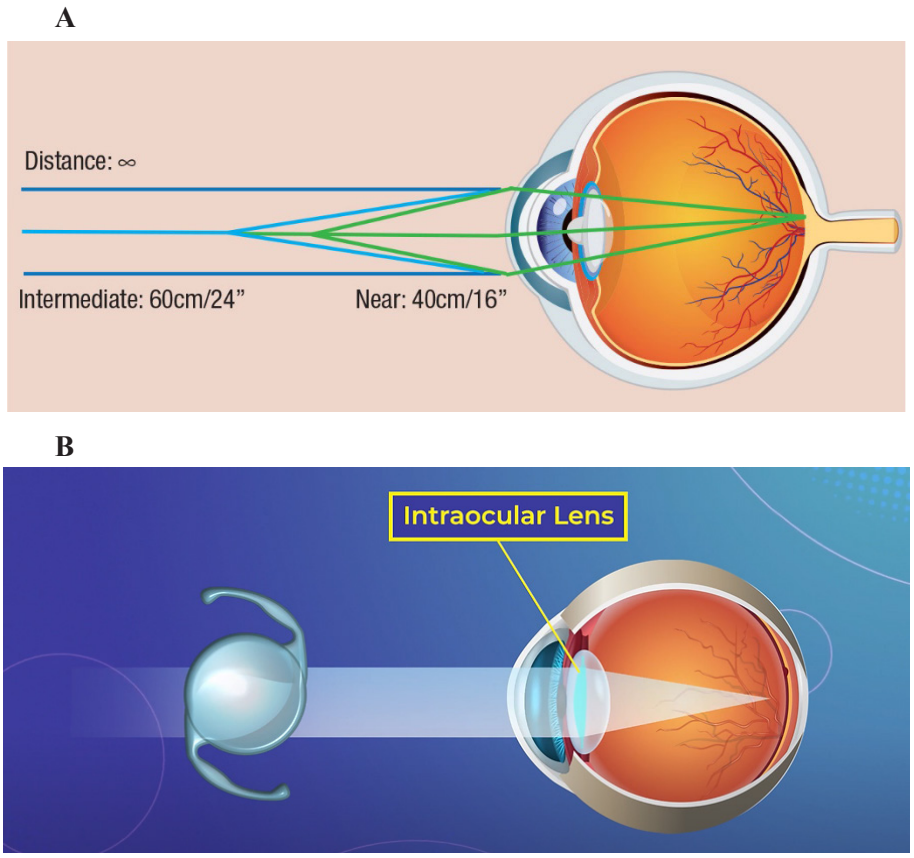
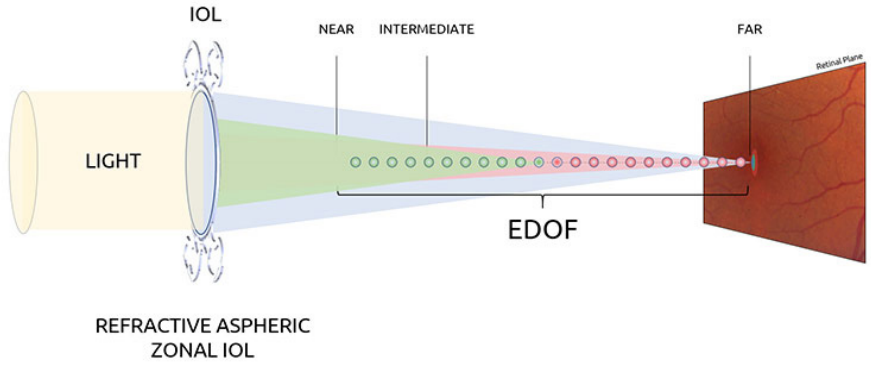


Figure 7: A: The performance of trifocal lenses
B: Focusing via trifocal lenses

Although diffractive bifocal intra – ocular lenses provide good visual acuity and contrast sensitivity at close and far distances, they are not sufficient at intermediate distances. For this purpose, trifocal intra – ocular lenses were formed by roughly the combination of two bifocal diffractive lenses. The power of the first order prism in these lenses was determined as +1.75 D on average. In this design, approximately half of the 20% beam leaving the +1.75 D prism is used in the +3.50 D prism and the beam loss is reduced. Thus, the first prism creates the intermediate distance at approximately 60 cm, and a close distance focus is created at 30 cm with the second row of prisms. Trifocal lenses have two close focus *(1st row of 1st lens and 2nd row of 2nd lens)* meaning 5% gain over bifocal lenses. This enables an intermediate focus *(1st row of the 2nd lens)* for 60 – 80 cm distance. With the evaluation of the 20% unfocused zone, the

lost area decreases to 14% and 25% increase in all light energy utilization is achieved compared to bifocals.

A



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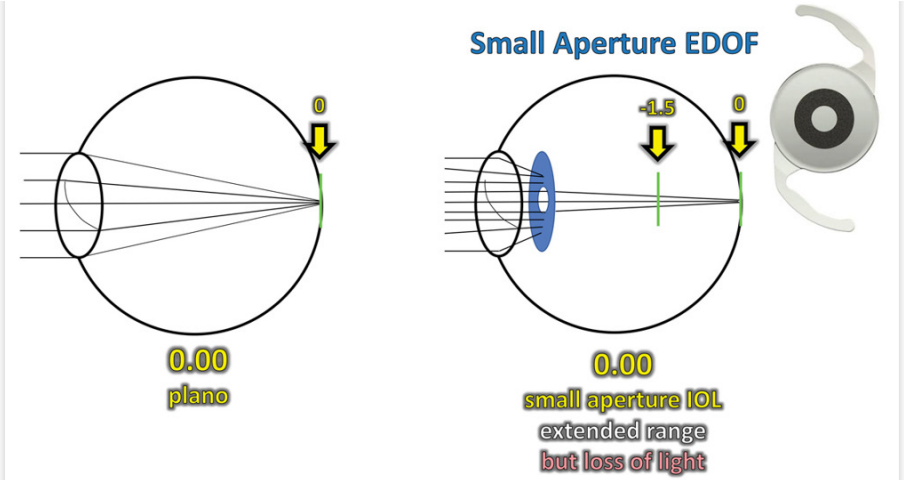

Figure 8: A: photic phenomena
B: understanding EDOF technology

EDOF *(expanded depth of focus)* technology has been developed to get rid of the halo and glare effect in trifocal lenses, to increase contrast sensitivity, and to provide uninterrupted clear vision. In these lenses, an expanded depth of focus is created instead of creating different focuses by sharing or scattering the light. This is achieved with the "echelette" design on its diffractive surface. In this design, the prisms are optimized to create a seamless image. EDOF lenses are biconvex and have an aspherical surface designed with Wavefront technology.

The back has an achromatic, diffractive, "echelette" design. With this design, it transmits almost all of the light to the retina and reduces chromatic aberrations.

Each lens design has its advantages and disadvantages. First the Mix-and-Match patients are expected to have poorer intermediate visual acuity, but better visual quality than compared to EDOF or trifocal IOL alone. EDOF lenses provide steady visual changes from far to near vision but a poorer near visual acuity than Mix-and-Match or trifocal IOLs . Third, the trifocal lenses have good far, intermediate, and near visual acuity however, more glare and halo symptoms. The logic that lies beneath the Mix-and-Match surgery is combining a trifocal IOL with an EDOF lens for better functional near vision with decreased photic phenomena.

The lifestyle and occupation of the individual should be taken into account between the patient and physician before lens selection. The outcomes of surgery is important to users of tablets, handheld devices or any other equipment. Quality of vision expectations should be managed in a patient centric approach.

Abbreviations:

D : Dioptry
EDOF : Extended Depth of Focus
FDA : Food and Drug Administration
IOL : Intra – ocular Lens
LOCSIII : Lens Opacities Classification System III
MFIOL : Multi focal intra – ocular Lens
MTF : modulation transfer function
ND – YAG : Neodymium-Yttrium-Aluminium-Garnet
OCT : Optical Coherence Tomography
Phaco : phacoemulsification
PMMA : poly-methyl methacrylate
PS : posterior segment
RLE : refractive lens exchange
RNFL : retinal nerve fiber layer
UV – B : ultraviolet – b
VA : visual acuity

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CHAPTER XIV

CONSERVATIVE SURGERY ON PLACENTA PREVIA ACCRETA SPECTRUM

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1. Introduction

Placenta previa is when the placenta completely covers the internal cervical os. Although its prevalence is 0.4%, its incidence varies regionally. The incidence is increasing with the increase in the number of cesarean sections all over the world. The most important risk factors seem to be previous placenta previa and previous cesarean section. In addition, advanced maternal age, multiparity and previous myomectomy operation and curettage are among the risk factors. Diagnosis can be made with a standard ultrasound examination.

Transvaginal ultrasonography is more effective in the diagnosis of placenta previa because the cervix can be evaluated more easily. In these patients, severe bleeding may occur both during pregnancy and during and after cesarean section. However, it has complications such as organ injuries (bladder or bowel), hysterectomy and maternal death.

The presence of placental invasion should be checked in patients with placenta previa. This situation, in which the placenta progresses into the uterine muscle wall, is called placenta previa-acreta spectrum (PAS), and the risk of bleeding and hysterectomy during surgery is quite high. The diagnosis of PAS is again made by ultrasonography. Findings helpful for diagnosis in a third trimester ultrasonographic examination are as follows. Loss of the normal hypoechoic retroplacental zone (clear zone), presence of the lacunar area in the placenta, diffuse or focal turbulent flow in the lacunae, interruption of the line between uterus and bladder, retroplacental myometrial thickness of <1 mm, Bridging vessels, increased blood supply between uterus and bladder in Doppler ultrasonography, protrusion of the placenta towards the posterior wall of the bladder.

Cesarean hysterectomy is recommended in the treatment, especially in patients with PAS. The most appropriate cesarean timing is between 34 0/7–35 6/7 weeks, especially for patients with placental invasion. The reason for the cesarean section before the 36th week is to avoid the risk of bleeding after this week. Cesarean section is recommended for these patients in centers where a multidisciplinary approach can be performed, such as anesthesiology, maternal-fetal medicine, neonatology, and specialist pelvic surgeons (such as gynecological oncology). Since the expected amount of bleeding during cesarean section is very high, it is recommended that blood products should be prepared before surgery in these patients.

In cesarean hysterectomy surgery, the baby is delivered with a fundal incision after entering the abdomen with a midline incision. The cord is clamped close to the placenta and released into the uterus. The uterine incision is then closed. The invading vessels on the bladder are ligated and the bladder is completely dissected from the uterus. Normal hysterectomy procedures are then performed. During these procedures, the hypogastric artery is usually ligated bilaterally.

Hypogastric artery ligation is a procedure that should be performed by experienced surgeons, and complications such as artery and evn ruptures may occur during the procedure. In addition, the process may not always be completed in a short time. In some patients, interventional radiology may be helpful for hypogastric artery embolization. However, this procedure is not possible in unstable patients. Despite the experience in cesarean hysterectomy operations performed in patients with placental invasion anomaly, this surgery, where blood loss is high, has serious complications such as major vessel injuries, bowel and bladder injury.

In addition to this treatment, conservative treatment options have been increasing recently. The aim of conservative treatment is to preserve the patient's possible fertility and to continue the monthly menstrual cycle. The most well-known and first applied method in conservative treatment is to leave the placenta in place and wait for its resorption. In addition, operations performed with various suture techniques, along with removal of the placenta from the uterus, have also been described.

2. Conservative Methods

2.1. Leaving the Placenta in Place

In this technique, after the baby is born, the cord is clamped close to the placenta and released into the uterus. In this conservative method, which was

first described, the uterus is closed like a normal cesarean section. Resorption of the placenta is expected over time. The waiting period is an average of 6 months (4-12 months). This method has major complications. These are delayed bleeding, endometritis, sepsis and disseminated intravascular coagulopathy. In one of the largest series of studies, the rate of uterine preservation was reported as 78% in cases where the placenta was left in place. In addition, it was stated that great artery ligation was performed in the majority of these patients. Half of the patients had postpartum hemorrhage and 22% required hysterectomy (between the first 24 hours and 3 months). In this study, serious complications such as maternal death due to aplasia, acute renal failure and septic shock were reported after methotrexate use. It was stated that hysteroscopy was performed to remove the placenta at an average of 20 weeks in 25% of the cases. In another study, bleeding, sepsis, and emergency hysterectomy were observed in 40% of cases in which the placenta was left in place. In this study, 119 percreta cases in the literature were compiled and compared with patients who underwent hysterectomy. Bladder injury was found to be higher in patients who underwent hysterectomy. It has been stated that the number of bleeding and cardiopulmonary arrest is higher in cases where the placenta is left in place. In a literature review including 517 patients, it was reported that 33.2% of the patients underwent delayed hysterectomy during the postpartum 12-month follow-up period.

In another study, the authors suggested drainage of the amniotic fluid before surgery. In this way, before the baby is delivered, the uterus can be completely removed from the abdomen and the baby will be delivered with an incision away from the placenta. In the study conducted with 5 patients, it was especially emphasized to pay attention to fetal heart beats during the procedure. It has been reported that reoperation was required in one of five patients due to postoperative obstruction.

There are also studies using methotrexate in patients in whom the placenta was left in place. Rapidly proliferating cells are the target of methotrexate, which is used in ectopic pregnancy and choriocarcinoma. It is an important handicap that it cannot be used in breastfeeding mothers. Currently, the use of methotrexate is not recommended due to unproven efficacy and serious complications such as pancytopenia and nephrotoxicity.

Studies in which the remaining placenta was removed by hysteroscopy were performed in patients in whom the placenta was left in place. Here, it is aimed to accelerate healing and reduce delayed bleeding. In the study in which hysteroscopic resection was applied to 12 patients, only 1 patient was

unsuccessful. It has also been reported that more than one hysteroscopic procedure is required for complete resection in patients. In a study examining conservative surgeries, it was reported that hysteroscopic resection of the placenta is not appropriate in cases of increta and percreta. In all these cases, entering the abdomen with a midline incision was the more preferred method. Entering the uterus through a fundal incision was important in terms of staying away from the placenta.

Due to reasons such as leaving the placenta in place, serious complications, delayed bleeding and hysterectomy, and long-term follow-up of the patient, there are currently question marks in terms of its effectiveness.

2.2. Shehata's Technique

This technique was defined by Ayman Shehata Dawood in 2019 and is also referred to as the 3-step technique. The first step is to connect the uterine artery bilaterally from the uterine isthmic region and 1 cm above the incision line, before separating the placenta. In the second step, after the placenta is removed, 2 quadruple sutures are placed in the lower uterine segment, and in the last step, a Foley catheter is placed through the cervical route to provide compression and drainage. After the 2nd step, the placenta was tried to be removed by hand completely or piecemeal. If the placenta did not detach, it was cut with scissors. In this study, which included 91 patients, the procedural success rate was 94.5%. While only 10 patients were reported to have percreta in the patient data, the total number of hysterectomies was reported as five. Apart from these five patients who underwent hysterectomy due to massive bleeding or uterine atony, bladder injury was reported as a complication in five patients. The inclusion of patients without cesarean section and cases with low lying placenta in the study shows great variability in case selection. The absence of any vascular intervention is the strength of the study. The major shortcomings of this study are the diversity in case selection and the lack of sufficient data on the effectiveness of this technique in patients with percreta.

2.3. Tripel P Procedure

This technique was first described in 2012. In this technique, which was used only in 4 patients when defined, the baby is delivered through a uterine incision over the upper border of the placenta and the cord is clamped in the first step. Inflating the balloons in the internal iliac artery, which was previously placed by interventional radiology, constitutes the second step. The aim here

is to reduce the blood supply of the uterus. In the last stage, the placenta is not touched. The area where the placenta is located and the myometrial layer are cut together with scissors and removed. In the study where 4 patients were reported to have percreta, bladder invasion was positive in all patients. The authors stated that the technique may be difficult to use in patients with Broad ligament invasion. This method was successful in all patients. In a study of 50 patients with this procedure, the success rate was reported as 100%. In the study, the authors reported the necessity of uterine artery embolization for postoperative bleeding in 3 patients, thrombosis developed in 3 patients with balloon placed in the internal iliac artery, bladder injury in one patient, and a patient re-operated as a result of bleeding from a vessel coming out of the bladder. In this study, the number of placentas invading up to the cervix was only 4 cases. The biggest handicap of this study, which included patients with anteriorly located placenta without previa, was the wide variety in patient selection. In another study discussing the Tripel P procedure, it is stated that this procedure is not a suitable option for cases with deep invasion of the broad ligament. In this case, it was stated that the options of cesarean hysterectomy or leaving the placenta in place may be appropriate. The inability of the procedure to be preferred in the presence of deeply invading placenta indicates that it is not suitable for conservative surgery in all patients with placenta previa.

2.4. Nausicaa Compression Suture Technique

This technique was described in 2019. In this technique, horizontal sutures placed on the anterior and posterior wall of the uterus after removal of the placenta are defined. Suturing is done after the baby is removed from an area distant from the placenta. Then, the entire placenta is removed with the help of an incision in the uterus. All areas where the placental bed was removed are sutured with this technique and the uterus is closed. There is a distance of approximately 1.5-2 cm between the stitches. During the suturing process, care should be taken not to stick the anterior and posterior walls of the uterus together. Suturing is performed both above and below the hysterotomy incision. This technique is named after the giant worm, a character from the Japanese movie 'Nausicaä of the Valley of the Wind'. It was reported that the technique was unsuccessful in 2 cases with placenta increta (97% success rate), and additional uterine artery embolization was performed in these two patients. In addition, uterine artery embolization was applied prophylactically to five patients postoperatively, while balloon occlusion was applied to the abdominal aorta temporarily during surgery

in five patients with advanced invasion. In this study, which was successful in all remaining cases, the authors stated that the technique would not work in cases with parametrial invasion. In addition, it was stated that intra-abdominal abscess developed due to uterine necrosis in 2 patients after surgery, and one patient was debrided by reoperation, and the other patient was treated by placing a drain under the guidance of computed tomography.

2.5. Hypogastric Artery Ligation and Endo-Uterine Hemostatic Suture Technique

This technique was described in a study of 38 patients in 2016. The abdomen is entered with a Pfannenstiel incision. The vessels behind the bladder are ligated with sutures or cautery and the bladder is carefully dissected. After opening the uterus from a non-placental region, the baby is delivered and the umbilical cord is clamped. The placenta is not touched. The hypogastric arteries are then ligated bilaterally. After the placenta is completely removed, cross sutures are placed on the placental bed to try to stop the bleeding. In the study, which included 38 patients in total, hysterectomy was performed in 6 patients, and the success rate of the technique was given as 84.3%. The authors stated that complications developed in a total of 5 patients, 1 vascular and 4 urinary. It is noteworthy that patients with deep invasion were not included in the study while selecting patients. It can be concluded that this method, for which no relevant explanation is given for exclusion, is not suitable for patients with deep invasion. It should not be forgotten that hypogastric artery ligation is a procedure that requires a special surgery and has serious complications.

2.6. Intracavitary Suture Technique

This technique was described in 2018. In patients with suspected placenta percreta, vascularization in the bladder was observed by performing cystoscopy during the operation. In patients with placenta accreta and increta, the baby is delivered by entering the uterus through an incision made from a region far from the placental invasion area. The placenta is then completely removed. In patients suspected of having placenta percreta, after the baby is delivered with a fundal incision, the hysterotomy incision is closed by leaving the cord inside the uterus without removing the placenta. The bladder is dissected by ligating the uterovesical vessels with cautery or sutures. In patients with placenta percreta, the placenta is completely removed from the uterus with a second incision. The bladder was deliberately opened in patients who could not undergo bladder

dissection. With a suture starting from inside the uterus, they are passed through the bladder and returned to the uterus, and then the suture is tied inside the uterus. For patients with posterior uterine wall invasion, a large diagonal suture to the posterior uterine wall was additionally used. In addition, before the technique was applied, uterine blood supply was tried to be reduced by clamping the proximal branch of the uterine artery and the utero-ovarian anastomoses. In the study, which included 62 patients in total, it was stated that 4 patients underwent hysterectomy after massive bleeding during bladder dissection. In the study where infection was observed in 5 patients in total after the surgery, the authors did not mention any other complication. The authors commented that this technique may be suitable for patients with fertility aspirations in the future. In the study, it was stated that the patients who underwent hysterectomy had severely invasive percreta cases and it was stated that they had bladder invasion. With this information, it can be interpreted that the technique is not suitable in every case of percreta.

2.7. Foley Balloon Tamponade Method

The method was described in a study conducted with 15 patients in 2011. After the placenta was removed from the uterus, roller gauze pack was applied to the lower uterine segment to temporarily stop the bleeding. Bleeding areas in the placental bed were tied with an 8-shaped suture. In cases where the bleeding did not stop, a foley catheter was inserted into the uterus and the tip was passed through the cervix and removed from the vagina with the help of an assistant. Care was taken not to pass sutures through the balloon while closing the hysterotomy incision. The foley catheter was then inflated to approximately 100 cc and moderate traction was applied. The success of this method is given as 100%. It was also stated that there were no complications after the procedure. The authors stated that they selected the cases included in the study from patients without advanced invasion. The usability of this method, which is stated to be easy to apply by the authors, in patients with advanced invasion has not been discussed. The small number of patients included in the study is another handicap of the study.

2.8. Multiple Interrupted Uterine Transverse Compression Sutures with Uterine Artery Ligation Technique

This technique was described in a study with 24 patients in 2017. The baby is delivered through a high uterine incision. The bladder is then dessected from

the uterus. The area below the incision line is sutured and tied, passing through both broad ligaments, including the uterine arteries. In this way, suturing is performed at 2-3 cm intervals until the incision in the uterus.

Both uterine artery ligation and uterine compression are performed. During this process, the authors stated that attention should be paid to the ureters. It is important to know that percreta cases were not included in the study in the article. In the study where 8 patients had atony cases, it was stated that the procedure was unsuccessful in 2 accreta cases and hysterectomy was required. The authors stated that the technique had a high success rate, except for hysterectomy performed on 2 patients with placenta accreta. No other complication was mentioned except in 3 patients who were reported to have bladder injuries. Although the suture technique described in the study is easy to apply, it is an important handicap that it is not preferred in percreta cases. In addition, the small number of patients indicates that studies with more patients are needed.

2.9. Uterine Segmental Resection Technique

In this technique, in which a total of 326 patients were included, the uterovesical vessels between the uterus and bladder are ligated, mostly by entering the abdomen through a Pfannenstiel skin incision and dissecting them up to the cervix. Afterwards, the baby is delivered by entering the uterus from a point away from the placental invasion. In the meantime, lower uterine bleeding areas are tried to be controlled with square sutures or by ligating the colpouterin vessel. The placental invasion area between the lower uterine segment and the incision is completely removed from the uterus. In the meantime, make sure that the entire placenta is removed. The remaining uterine tissue is then closed. In this study, patients were divided into 4 groups according to their invasion status. Patients with upper bladder in group 1, parametrial invasion in group 2, lower bladder invasion in group 3, and patients with lower bladder invasion and fibrosis in group 4 were included. Infrarenal aortic balloon placement was added to the surgery, especially in patients in the 3rd and 4th groups, as the risk of bleeding was predicted to be high. In patients with heavy bleeding, the bleeding was tried to be stopped by either manually pressing the aorta from the sacral promontory level or by inflating this balloon. In the study, the authors found the uterine preservation rates to be 81.5%-47.7%-21.8% and 0%, respectively. Complications such as bleeding, total urinary complications and bladder opening were observed to increase gradually in the 4th group. In addition to these

complications, complications such as ureteral injury, disseminated intravascular coagulation, hypovolemic shock, and reoperation were observed in the patients included in the study. This technique appears to work best in patients with placenta invading the upper bladder. At lower levels the success of the technique decreases. In addition, it is seen that the complication rate increases as the degree of invasion increases in surgeries performed with this technique.

The technique performed in another study describing segmental uterus resection is similar to the above technique, in addition, after bladder dissection, a hole is made bilaterally from the broad liament at the level of the cervical internal ostium and ligated with a Foley catheter. The purpose of this procedure is to ligate the uterine artery and reduce bleeding by performing a tourniquet from the cervical region with a foley catheter in cases of bleeding after removal of the invading placenta from the uterus. In the study, which included 21 patients, the authors stated that only 2 cases required hysterectomy, and the success rate of the procedure was 91.3%. Massive bleeding during bladder dissection was reported in 2 patients who underwent hysterectomy. In the study, which stated that hypogastric artery ligation was not performed in any patient, the uterine artery was ligated bilaterally in all patients. The authors stated that there were no other complications in the patients. Although the success of the study seems high, the small number of patients included in the study and the fact that the invasion degree of the patients was not specified are the shortcomings of the study.

The incidence of placenta previa increases with the increase in the number of cesarean sections. In this case, we will encounter more cases of placenta previa and accreta.

Hysterectomy, which will be performed at a relatively young age, results in the end of fertility of the patients. Accepting this situation will be very difficult for families who want children. In addition, there will be psychological effects of organ loss at an early age. In these cases where the risk of mortality and morbidity is high, the importance of uterine-sparing surgery increases for women who want to maintain their fertility. It is clear that obstetricians should work on researching surgical methods that are easy to perform and have less complications.

In cases where the placenta was left in place, the patient had to be followed for a long time in the postoperative period. Although the rates of delayed bleeding-induced hysterectomy in patients differed according to the studies, they were quite high. However, there are many publications in the literature stating

that there are patients presenting with disseminated intravascular coagulopathy after a long period of time. Among other methods, a method that is effective in all cases of placenta previa and percreta has not been described. Studies show that additional surgical methods or interventional procedures are required.

Most of the techniques mentioned above require tertiary hospitals (for reasons such as multidisciplinary approach, advanced surgical expertise). It is clear that more work is needed to find new techniques that can be used in peripheral hospitals and that we can use in all cases of placenta previa.

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CHAPTER XV

INNOVATIVE PERSPECTIVE IN PROSTATE CANCER TREATMENT

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Prostate cancer was first described in the middle of the 19th century. The research at the time stated that this disease was "a very rare disease". Remarkably, prostate cancer has become a serious health issue 170 years later. The fact that prostate cancer is becoming more common has led to big changes in how it is found and treated over the past century. In 2020, prostate cancer is detected to be the second most often diagnosed cancer in males, with an estimated 1.4 million new patients globally. The prevalence of PCa at age 30 years was 5% (95% confidence interval [CI]: 3–8%), increasing by an odds ratio (OR) of 1.7 (1.6–1.8) each decade to a prevalence of 59% (48–71%) by age > 79 years.

This significant rise in prostate cancer incidence may be linked to a variety of factors. The most important reason is that, before the early 1900s, prostate cancer was not distinguished from other causes of urinary obstruction. Moreover, prostate cancer incidence grows more significantly with age than any other cancer type. The instances have increased over the previous century as the average life expectancy has improved. Also, the rise in prevalence seems to be connected in some manner to "Western" lifestyles. The incidence of clinical prostate cancer is much lower in Asian populations than in Western ones, and it rises in males who migrate to Western countries, reflecting an environmental or nutritional factor. This growing prevalence has resulted in remarkable advances in prostate cancer detection and therapy in the last century.

Even in the absence of any symptoms, a prostate biopsy is performed when an elevated PSA is detected, especially in elderly men. In these patients, low-risk prostate cancer is frequently diagnosed. In spite of the fact that disease-free survival increases with early and effective treatment in patients with low-risk

diseases, morbidities resulting from treatment are common. There is a risk of impotence, incontinence, infection, thrombosis, and damage to nearby organs, especially in patients who are treated not only in the area where the cancer is, but also for the whole prostate. The majority of patients with low-risk diseases die from causes other than prostate cancer, but the prognosis of such patients cannot be predicted. So, the goal is to reduce the possible side effects of prostate cancer treatment by using focal prostate cancer treatments and making changes to existing treatments for some types of prostate cancer that are minimal invasive.

1. Imaging Methods

Magnetic Resonance Imaging (MRI) is the most effective imaging technique for detecting prostate cancer. Several studies have demonstrated that the use of an endocoil with MRI improves treatment efficacy by increasing image quality. Similarly, widespread use of 3T MRI has had a positive impact on imaging for prostate cancer. Even though the models and methods used in published studies can change how sensitive and specific they are, MRI is still the most sensitive imaging method for diagnosing prostate cancer.

As a transmembrane protein unique to the prostate epithelial cell membrane, prostate-specific membrane antigen (PSMA) is extensively expressed in more than 90 percent of PCa cells and rises with tumor invasion, metastasis, and recurrence. In the last few years, research has shown that 68Ga-PSMA positron-emission tomography/computed tomography (68Ga-PSMA PET/CT) may improve diagnostic accuracy and staging, as well as identify the biochemical recurrence of prostate cancer. 68Ga-PSMA PET/CT may identify more recurring and metastatic lesions than MRI. PET/CT with 68Ga-PSMA is a relatively recent technology. The early diagnostic trial findings are quite promising.

2. Prostate Biopsy

The gold standard method for diagnosing prostate cancer is a prostate biopsy. Because imaging methods are used more, people have more experience with them, and their effectiveness gets better. As a result of this advancement in imaging techniques, transrectal ultrasound-guided prostate biopsies have been developed, and their use has increased. Standard prostate biopsies are performed under transrectal ultrasound guidance. Although transrectal ultrasonography-guided prostate biopsy (TRUSG) is the standard method of diagnosis, it has a very high rate of false-negative results. Moreover, some patients require repeat

biopsies, which increases the incidence of complications. This has led to the development of targeted biopsies with a higher success rate for diagnosis.

Transperineal in-gantry MRI-targeted prostate biopsy under MRI with MRI-compatible templates has been shown to have a high diagnostic value for finding prostate cancer, especially in patients with a high suspicion of prostate cancer but no prostate cancer found in a previous prostate biopsy.

3. Treatment

3.1. Local Treatment

Since low-risk prostate cancer carries a minimal risk of cancer-related death and whole prostate gland treatments decreases patients' quality of life, the theory that local treatments can be administered to suitable patients has emerged. Thus, subtotal surgical methods were studied and used for the treatment of prostate cancer. Imaging-guided focal ablation techniques include focal brachytherapy, laser interstitial thermal therapy (LITT), high-intensity focused ultrasound (HIFU), cryotherapy, and the gamma knife. These treatments, which can be administered to patients with limited prostate disease, are debatable in terms of which patients should receive focal treatment regardless of the technique. It is known that, in addition to the lesion detected by screening, there may be additional, smaller lesions in the prostate due to the multifocal nature of prostate cancer. Additionally, the risk of extracapsular spread cannot be disregarded.

Brachytherapy is a prostate-sparing treatment for prostate cancer that involves seeding radionuclide material inside the prostate's cancerous region. This treatment, which has proven oncological efficacy over the long term, can be administered alone or in combination with radiotherapy. Once more, as a result of the MRI of the treatment procedure and technological advancements, the application of treatment has become easier, and treatment success has increased. Small robotic devices that are MRI-compatible and allow the placement of radionuclide materials under 7T MRI allow for more sensitive and effective placement. Studies and developments continue on this subject.

3.2. Robotic Surgery

Surgery for prostate cancer can be performed openly, laparoscopically, or robotically. Open prostate surgery has been an effective procedure for a long time, but it is gradually being replaced by robotic prostate surgery, which has superior surgical success rates and fewer complications. Laparoscopy, which

is preferred for abdominal organ surgery due to its safety, began to be used for prostate surgery at the end of the 1990s. But because of technical problems, laparoscopic prostate cancer surgery was not preferred, and laparoscopy was not widely used in prostate surgery. Since the introduction of robotic surgeries in the early 2000s, the use of this treatment in prostate surgeries has increased rapidly. Its success in prostate surgery, which is very difficult to reach due to its location and requires fine skill, has also increased in a short period of time. However, open prostate surgery for cancer is now preferred to robotic surgery due to the patient's comfort and urinary continence after surgery, as well as cancer treatment success. Nowadays, in many centers around the world, robot-assisted laparoscopic radical prostatectomy (RaLP) is now a routine surgical procedure.

Although the surgery is referred to as "robotic," "computer-assisted surgery" is a more appropriate term. Because it must be able to control itself in order to be a robot, but this requirement is met by a computer-dependent operator.

Before it was used in urology, robotic surgery was used in areas like neurosurgery and orthopedics where precise surgery and clear landmarks were needed. These are stereotactic devices containing the patient's cranial computed tomography images. This allows for the complete and safe removal of brain tumors, as well as the support of biopsies. Another robot is used in orthopedics to drill holes in the femur for implant placement.

It did not take long for robotic surgery to be performed on the prostate, a fixed organ in the pelvis where endoscopic treatment played an important role after the advent of robotic surgery. PROBOT, which was developed in 1989, is the first robotic system adopted in urology. This robot was incising the resection area determined by the surgeon based on ultrasonic images. Following the incision, the surgeon performed the hemostasis procedure. This surgery, however, has not been widely used.

PAKY, a robot that allows kidney biopsies to be done from a distance, was made so that the surgeon doesn't have to be exposed to as much radiation during irradiated kidney biopsies. So, the surgeon can do a kidney biopsy without being exposed to radiation in the operating room by controlling the robot from a radiation-protected room. However, it has not been widely utilized because this robot's success rate in entering the desired location is insufficient.

AESOP, the laparoscopic camera robot, is the first robot approved by the Food and Drug Administration of the United States (FDA). The voice-controlled

version of AESOP, called ZEUS, has been made, but it is not very popular because of the difficulty in detecting and applying voice commands, especially in important situations, and its lack of speed.

After Zeus, a prototype MONA was made that could also control robotic arms in addition to the camera. Da Vinci, which has three arms that can be switched out, became the only surgical robot after the others were put out of service. In addition to the 3-D image and seven-angle camera movements, da Vinci allows the use of two or three robotic arms, depending on the situation, whereas the updated model provides the option of a fourth arm, as well as greater mobility and higher resolution imagery. The system's high cost and lack of tactile stimuli are also limitations.

Laparoscopic radical prostatectomy is done by skilled hands using robots that can move in two dimensions and four angles. However, many challenges will prevent its widespread adoption. Robotic advancements, fueled by advancements in laparoscopy, have primarily been used in prostate surgery, among other urological procedures. The Da Vinci robot enables transperitoneal or extraperineal prostate surgery. Therefore, it is impossible to advocate one surgical technique over another. RaLP was shown to have shorter hospital stays and less blood loss than open radical prostatectomy (RP), but not better results in terms of function or cancer after 3 months. Increased surgical experience has decreased RP complication rates and enhanced cancer treatment. Lower rates of positive surgical margins among surgeons who do a lot of surgeries show that experience and paying attention to the details of surgery might make it easier to treat cancer with RP. Even though there was a lot of methodological uncertainty, RaLP had less pain during surgery and a lower rate of positive surgical margins than laparoscopic prostatectomy (LRP). In the RARP group, there were greater rates of erectile function recovery (RR: 1.51, 95% CI: 1.19–1.92) and continence function recovery (RR: 1.14, 95% CI: 1.04–1.24). Still, a Cochrane review that compared either RARP or LRP to open RP used randomized controlled trials and found no significant differences between the groups in terms of cancer, urinary quality, and sexual function. On the other hand, both RARP and LRP led to statistically significant improvements over open RP in terms of hospital stay length and blood transfusion rates. Robotic prostate surgery can now be done with a number of new robots in addition to the Da Vinci brand.

Although flexable robots, which are primarily used in cardiological interventions, are implemented for endocoscopic surgeries in urology, there are also efforts to contribute to the robotic prostate surgery that is currently

in use. Using a parallel cylinder or hydraulic cylinder to move the quadruped standard robot toward active compliance is another option; however, this would considerably increase the complexity of the control and the weight of the robot's body, limiting it from being tiny or medium-sized. Three-dimensional passive compliance offers a solution to this issue. The construction is very adaptable, lightweight, and has a straightforward stiffness and leg length adjustment. Unlike previous rigid-flexible linked quadruped robots, this robot's stability in all directions does not need a sophisticated algorithm. Currently, many difficulties encountered by medium-sized quadruped robots are connected to these traits, such as small weight, easy control, and excellent stability. Also, coupled rigid-flexible-soft robots are an important research trend in robotics, but their design, production, and modeling present several theoretical and technological difficulties. Inspired by fishbones, an unique cable-driven single-backbone continuum robot with a compact shape, low weight, and great dexterity was presented. In contrast to previous continuum robots with a single backbone, the central backbone of the proposed continuum robot is serially created by numerous bio-inspired fishbone units organized in a cross-pattern. The suggested bioinspired fishbone unit is primarily a particular rigid-flexible-soft construction with excellent one-dimensional bending capabilities. The distinctive design and construction of the middle backbone give the continuum robot superior constant curve characteristics and reduce the coupling between different motion dimensions, laying the groundwork for the continuum robot to have a more accurate theoretical model as well as regular and controllable deformation. In addition, a comparison of practical and theoretical data reveals that the kinematics model's prediction errors are within the intended range of 0.5 mm. In addition, the relationship between the cable driving force of the bio-inspired fishbone unit and its bending angle was discovered, which may give future advice for optimizing the continuum robot.

In the last few years, developments in therapeutic endoscopy and minimally invasive surgery have led to the convergence of approaches for treating a variety of illnesses. Concurrent with the development of multichannel, flexible endoscopes with unique image manipulation techniques such as narrow band imaging and autofluorescence, more sophisticated therapeutic endoscopy techniques such as endoscopic mucosal excision and submucosal dissection have become a reality. These approaches make endoscopic treatment of more illnesses, including cancer in its early stages, conceivable than was previously possible. Using a mix of laparoscopic and endoscopic procedures, it

was possible to undertake significant intra-abdominal treatments via naturally occurring orifices, avoiding the need for skin incisions. This was the logical progression of these techniques. Miniature robots currently used for imaging luminal organs offer hope for their future application in surgical procedures. NOTES (natural orifice transluminal endoscopic surgery) is the suggested term for endoscopic surgery conducted with tools that acquire access via a natural orifice. Although endoscopic surgery and extraluminal organ surgery are very different surgical procedures, it is believed that miniature robots will be utilized in both in the future, and studies are currently being conducted to support this prediction. NOTES operations are conducted using tools in one bodily cavity, often the peritoneal cavity, via a natural entrance as opposed to a percutaneous incision. Hybrid NOTES operations combine the NOTES method with direct transcutaneous access to the cavities, often in conjunction with laparoscopic instruments. Much of the current concern about NOTES is based on the fact that the procedure creates iatrogenic harm with the potential for immediate or delayed complications. Infection, hemorrhage, visceral damage, and delayed anastomotic or entrance site leaks with potentially serious outcomes are among these dangers. Despite the fact that laboratory studies indicate that the danger of introducing infection is minimal, it must be quantified in detail. Due to the location and orientation of the endoscope and the present state of hemostatic technology, vascular damage during access or a procedure may go unnoticed and be difficult to prevent. Visceral damage is also a recognized issue, and both the capacity to diagnose and treat any harm must be thoroughly considered. In addition to post-NOTES dyspareunia, long-term problems such as adhesion formation must also be assessed. Although there are several grounds for doubt, both the medical community and the general public have an obvious interest in this topic. NOTES has sparked a healthy and robust debate in the surgical communities about the introduction of a completely novel approach to surgical treatment. Concerning the hazards, genuine advantages, and expense of NOTES, several concerns remain unresolved. NOTES must be satisfactorily completed before they can be implemented in patients.

4. Artificial Intelligence

The digitalization and storage of large amounts of medical data have promoted the use of artificial intelligence-based solutions for diagnosis and management in the healthcare system. Artificial intelligence (AI) is an automated computer process with programmed intelligence built in that is used to make

decisions in a foreign environment. Commonly, the term "artificial intelligence" is used to describe robotic processes that are comprised of computer algorithms linked to production hardware. With advances in artificial intelligence, such as the creation of machine learning (ML) algorithms and deep learning (DL) models based on mathematical principles and statistical assumptions, robots may be programmed or educated to comprehend the underlying patterns or information within a given dataset. These complex algorithms have enabled AI based systems to forecast events effectively without being specifically intended to do so.

4.1. Artificial Intelligence in Prostate MRI Detection

Multiple studies have shown that MRI is an excellent approach for distinguishing clinically relevant PCs from insignificant PCs. It arose as an alternative to ultrasonography-guided transrectal biopsies for directing the pathologist to the exact place for removing tissue samples. MRI is often used to diagnose the stage of cancer by capturing imaging data that demonstrates the disease's progression outside the prostate. These images include very detailed data that is sometimes difficult to understand. Using an AI-based machine-learning system, this procedure may be mechanized with improved precision. It has been suggested that artificial intelligence might aid in detecting and recognizing prostate cancer, since the MRI result has early diagnostic importance. It is crucial to differentiate between aggressive and nonaggressive types of PC owing to their vastly varied prognoses. Prior to a biopsy, the European Association of Urology (EAU) advises the use of multiparametric MRI, an important diagnostic step that has been followed in several investigations. In addition, the predictions provided by these ML systems should aid physicians in reaching the ultimate judgment rather than entirely negating their interpretation. In light of the increase in prostate cancer cases, there is a need for AI based computer-based methodologies for the enhanced and rapid evaluation of prostate MRI data. For the increased identification and bi-parametric categorization of prostate MRIs, an AI system based on cascade deep learning was built, and the Prostate Imaging Reporting and Data System (PI-RADS) score was employed.

4.2. Artificial Intelligence in Prostate CT Detection

By examining normal computed tomography (CT) pictures, an artificial intelligence (AI) program was developed to identify early prostate cancer signs. Examining asymptomatic patients with and without prostate cancer

using CT scans to detect the disease's features led to the development of the AI system. However, the radiologists had difficulty identifying prostate cancer in the CT pictures. Due to the high radiation dosages, which may have long-term consequences, this method is not suggested for a typical cancer diagnosis. AI technology may be used to test for cancer in males diagnosed with various issues in the abdomen or pelvis. The AI algorithm was taught to search for disease indicators in a variety of scans and to identify the inspection region in the picture, thereby removing the need to manually edit the input photos. The AI algorithm improved the results and aided in the rapid identification of cancerous growths. Furthermore, with each scanned image, the AI technique improves, learning to understand the scans and detecting even the smallest irregularities; this technology has the potential to greatly improve prognoses. However, its biggest flaw is its poor sensitivity. In CT scans, the contrast between the prostate and the surrounding tissues is insufficient to distinguish the prostate from the other tissues. However, CT scans may identify the progression of prostate cancer to bone tissue and establish whether prostate brachytherapy is necessary.

4.3. Artificial Intelligence in Prostate Biopsy Sample Detection

Histological evaluation of a biopsy sample may include chemical treatment or freezing prior to section preparation for observation under the microscope, depending on the procedure. However, the whole testing procedure is laborious, time-consuming, and needs great accuracy. In contrast, due to a shortage of urological pathologists, the available human resources are insufficient to manage the large number of samples collected for a prostate cancer (PC) examination. This creates a scenario in which the examination may be done in whole or in part by an artificial intelligence system. A model based on deep learning (DL) was created to enhance the Gleason score for prostate cancer slides collected after prostatectomies. On the validation dataset, the DL algorithms produced a higher accuracy rate. This approach demonstrated the direct use of deep learning in picture classification and compared it to the human eye detection method.It was found that the pathologist was able to make observations in less time with the help of AI. In addition, the use of AI decreased the final findings' inconsistency.

4.4. Artificial Intelligence in Prostate Biopsy

Transrectal ultrasound biopsy (TRUS) is used to get a comprehensive image of the prostate gland and surrounding tissues. Prior to the development of imaging tools such as MRI, TRUS was the gold standard for guiding needle

biopsies for prostate cancer. Producing low-contrast images, TRUS has a limited sensitivity for detecting and staging prostate cancer. However, when compared to MRI, TRUS is less expensive, more convenient in the office, and delivers a real-time view. To accurately predict prostate cancer, MRI-TRUS fusion-guided needle biopsies have been created as a result of advances in prostate cancer detection. The approach has enhanced the rate at which MRI-TRUS fusion-guided biopsies are performed to target malignant lesions. The use of TRUS in a deep neural network to predict prostatic, zonal, and lesion segmentation in PC patients In this instance, the MRI-TRUS fusion-guided biopsy method aids physicians in identifying malignancies that traditional prostate biopsies may miss. It is able to do targeted biopsies by concentrating directly on the troublesome locations using enhanced MRI and ultrasound fusion imaging.

4.5. Artificial Intelligence in 3D Prostate Pathology Detection

The pathological analysis of biopsies and surgically excised tissues is essential for the diagnosis and characterization of the illness. Recent advances in the use of whole-slide imaging scanners by a number of clinics that have started digitizing their whole pathology processes, along with significant gains in processing capacity, have led to the growth of digital pathology methodologies in cancer and other fields. The combination of multiparametric MR-US image data with biopsy trajectory-proven pathology data was utilized to train the AI in the research on an AI strategy for the 3D prediction of PCa. The AI prediction was much higher than the radiologist's reading, and it was consistent with the data from the clinically significant cancer center (CSCa) when the RaLP specimens were used. The CSCa volumes predicted by the AI were more accurate than the radiologist's findings. In addition, separate research developed a technique for the non-destructive 3D pathology and computational analysis of all prostate samples that are tagged with a rapid and inexpensive fluorescent equivalent of standard hematoxylin and eosin (H&E) staining. This analysis is based on interpretable glandular features and is made feasible by the development of image translation-assisted 3D segmentation (ITAS3D). ITAS3D is a deep learning-based method for volumetrically segmenting tissue microstructures in an annotation-free, objective (biomarker-based), and immunolabel-free manner. In a risk evaluation of patients with low- to intermediate-risk prostate cancer, the 3D glandular characteristics of the cancer biopsies beat the identical 2D features based on clinical and biochemical recurrence outcomes.

4.6. Artificial Intelligence in Genomics and Proteomics Prostate Cancer Detection

PSA testing has enabled the detection and prognosis of prostate cancer. While many of these biomarkers have been studied and defined according to the purpose of each test, there is no usual overlap between these tests, and there is no perfect list of biomarkers used to predict the diagnosis and prognosis of PC. Therefore, it is crucial to develop and assess novel biomarkers of clinical importance in a reliable and relevant way. Thus, AI may be advantageous for evaluating these biomarkers. Ki67 and DLX2 are substantial markers of survival and disease progression, as well as significant predictors of future metastases, according to a number of studies. However, despite their high specificity for prostate cancer, their sensitivity is modest. In addition, the optimal strategy is multi-omics, in which genomic, transcriptomic, and metabolomic data must be merged and supplied to machine learning algorithms. Standard prediction models always have a high level of interpretability but limited accuracy. Overfitting is an additional constraint or worry for the deployment of a fully linked, dense network. However, overfitting may be controlled by the use of regularization methods, although at the expense of substantial computational effort. The genetic sequence is directly or indirectly reflected in biological phenotypes. The biological sequence data are extensive; thus, a deep learning technique is appropriate for analyzing these data and determining the link between sequence patterns and the phenotypic features of cancer. Here, the sequencing data may facilitate the diagnosis of malignant tissue at an early stage. Deep learning applied to genomic sequence data is commonly referred to as "genomic deep learning" (GDL). It establishes the connection between sequence variation and cancer-associated characteristics. It is shown that prediction performance is enhanced by building cancer-type-specific models. A public tool was developed to directly apply deep learning algorithms to the biological sequence. The patient's DNA sequence is used by the machine learning model to categorize cancer patients. In addition to gene expression, proteomics data might be useful for identifying potential biomarkers. New noninvasive biomarkers may be identified via computationally driven proteomics. It has been shown that AI may assist in more efficient biomarker selection and validation, which may help with prostate cancer surveillance.

4.7. Artificial Intelligence in Prostate Cancer Treatment Algorthm

The decision about the best prostate cancer treatment choice is crucial and requires careful consideration. Because combination therapies for oncological management are associated with a rise in complications and high morbidity rates, As a result, a multiparametric examination of both the patient and the illness features is required. As doctors are required to manage vast quantities of data ranging from macro-level physiology and behavior to laboratory investigations and, increasingly, "omic" data, AI is the best way to construct a prediction model using this data. The capacity of artificial intelligence to handle this complexity has outpaced human accuracy and management techniques. It aids physicians in comprehending the patient's situation accurately. There is a prediction software in which the patient's medical data was utilized to construct a prediction model using random forest ML methods, which may further aid in making treatment choices. If a huge collection of patient records is accessible, a deep network could be investigated. Multiple ML approaches must often be evaluated and compared before a model is finalized. The data characteristics decide whether basic or advanced ML models are appropriate.

In addition to all of these advances in AI, research is ongoing to ensure that all or a part of robotic prostate cancer surgeries are performed by AI. In the future, robots will be able to perform surgery more independently.

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