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Spiritual and Material Causes of Humanity's Diseases and AI Medicine

Evgeniy Bryndin[1]

[1] Interdisciplinary Researcher of the International Academy of Education, Novosibirsk, Russia
Correspondence: Evgeniy Bryndin, Interdisciplinary Researcher of the International Academy of Education, Novosibirsk, Russia.

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Abstract

The spiritual cause of human diseases is the rejection of harmonious relations with nature and the transition to immoderate consumption and comfort. Humanity views nature as a consumable material, and as a result, imperfect humanity relentlessly pollutes nature. Pollution of nature is the material cause of human diseases. Pollution of water and soil creates conditions for the emergence of infectious parasites. Inhabitants of reservoirs and soil are carriers and distributors of infectious parasites. Humanity, consuming inhabitants of reservoirs and soil, becomes a carrier of infectious parasites, a distributor of infections and a source of epidemics. AI medicine is developing to quickly and effectively treat rapidly spreading human diseases and prevent epidemics.

Keywords: spiritual and material causes, pollution of nature, human diseases, AI medicine

1. Introduction to the Problem

When unspiritual humanity defiles Nature, then Nature defiles humanity with diseases. Diseases are nature's response to its defilement by humanity. The emergence of diseases as nature's response to its defilement by humanity is a complex and multifaceted topic. On the one hand, diseases can be viewed as a natural response of ecosystems to disturbances caused by human activity, such as environmental pollution, climate change, destruction of natural habitats, and overexploitation of resources. Existing diseases can be the result of the interaction of various factors, including genetic predisposition, infectious agents, and people's lifestyles. For example, many diseases from viruses and bacteria can arise and spread due to changes in ecosystems caused by human activity.

It is important to note that the emergence of diseases as a response of nature is a spiritual biological law (Evgeniy Bryndin, 2018; Bryndin E.G. & Bryndina I.E., 2020; Evgeny Bryndin, 2024). Nature has no conscious intentions, but the changes we make to the environment lead to undesirable consequences, including the emergence of new diseases. Thus, it can be said that there is a relationship between the actions of humanity and the health of the population, and this topic requires deep analysis and awareness of the responsibility for the preservation of nature and the health of future generations (Bryndin E.G. & Bryndina I.E., 2019; Bryndin E.G. & Bryndina I.E., 2019; Evgeniy

Bryndin & Irina Bryndina, 2019; Evgeniy Bryndin, 2020; Bryndin E. G. & Bryndina I. E., 2020).

At the present stage, intelligent digital polyclinics are being formed — a modern medical institution that uses digital technologies and artificial intelligence to optimize the processes of diagnosis, treatment and patient care. An intelligent digital polyclinic offers innovative solutions to improve the quality of medical care and improve interaction between patients and doctors, managers with medical staff, between medical institutions.

2. Spiritual Aspects of Pollution of Nature by Humanity

First of all, we need to look at the pollution of nature by humanity through the prism of spiritual aspects. Here are some spiritual reasons that explain this phenomenon:

2.1 Alienation from Nature

Modern society perceives nature as a resource that can be used and exploited. This alienation leads away from harmonious relations with nature and leads to a lack of respect for the surrounding world and its ecosystems.

2.2 Materialism

Consumer culture places emphasis on material values and satisfaction of needs, which leads to ignoring environmental consequences. The spread of materialism reduces the level of responsibility for the environment.

2.3 Weakening of Spiritual Values

In the context of rapid technological progress and urbanization, many people lose touch with spiritual and moral values, such as caring for nature, harmony and gratitude. This leads to indifference to environmental issues.

2.4 Conflict Between Nature and Humanity

Nature is not seen by humanity as a friend and as part of a whole. This contributes to the perception of the environment as something that needs to be subdued and controlled.

2.5 Short-Term Thinking

The desire for immediate satisfaction of needs and the desire for quick results hinders long-term planning and care for the future of the planet.

2.6 Unawareness and Misunderstanding

Many people simply do not realize how their actions affect the environment. Spiritual unawareness and lack of understanding of the pollution of the planet by humanity as the cause of diseases.

2.7 Lack of Responsibility

Lack of understanding of one's role in the ecosystem and lack of a sense of responsibility for actions lead to pollution of nature.

3. Material Aspects of Environmental Pollution

Pollution of nature by humanity with harmful material substances and waste in various forms and shapes has made it a hostage to diseases.

3.1 Humanity Creates Infections by Polluting Nature with Harmful Waste

Pollution of nature with harmful waste does indeed contribute to the emergence and spread of infections. When waste, especially hazardous or toxic waste, gets into the environment, it can have serious consequences for ecosystems and human health. Let's look at several aspects of this problem.

3.1.1 Water Pollution

Runoff and waste containing pathogens contaminate drinking water supplies. This can lead to outbreaks of waterborne diseases such as cholera and many others.

3.1.2 Soil and Agriculture

Harmful substances and toxins can accumulate in the soil, which negatively affects crop yields and food quality. Since contaminated food becomes a source of infections, this poses a risk to human health.

3.1.3 Contact with Wildlife

Pollution disrupts natural ecosystems, leading to changes in animal behavior and migration. This can increase contact between wildlife and humans, increasing the risk of zoonotic disease transmission.

3.1.4 Development of Resistant Pathogens

Chemicals contained in waste can promote the development of antibiotic-resistant strains of bacteria, which creates additional difficulties in treating infectious diseases.

3.1.5 Decreased Biodiversity

Pollution can lead to declines in populations of various species, which disrupts the ecological balance and can facilitate the spread of pathogens.

3.2 Emergence of Infections in Nature

Emergence of infections in nature is related to

many factors, including ecosystem interactions, the evolution of pathogens and their hosts, and environmental conditions. Infectious diseases occur when pathogens such as bacteria, viruses, fungi, or parasites are transmitted from one organism to another. Let us consider several key aspects of infection.

3.2.1 Pathogens

Microorganisms that can cause disease. They can be found in the environment, in hosts (humans, animals, and plants), or in soil and water.

3.2.2 Pathogen Hosts

Organisms in which pathogens can multiply. Hosts can be either natural reservoirs of infections (e.g., wild animals) or susceptible to infections (e.g., humans).

3.2.3 Transmission of Infections

Infections can be transmitted in a variety of ways, including by aerosols (airborne droplets), contact (through the skin or mucous membranes), insect bites (e.g., mosquitoes), or contaminated food and water.

3.2.4 Pathogen Evolution

Pathogens can adapt and evolve to survive better in their hosts or to find new ways of being transmitted. This can lead to the emergence of new strains or even new species of pathogens.

3.2.5 Ecosystem Factors

Changes in ecosystems, such as climate change, habitat destruction, or animal migration, can facilitate the emergence of new infections. For example, climate change can expand the range of vectors such as mosquitoes, which can lead to the spread of diseases.

3.3 Path of Infections from Nature to Humans

The path of infections from nature to humans can be complex and multifaceted. It includes several stages, starting with the initial reservoir of infection in the wild and ending with infection of humans. Let's consider the main stages of this path:

3.3.1 Reservoir of Infection

These are organisms (animals, plants, microorganisms) in which the pathogen (bacteria, virus, fungus or parasite) can survive and reproduce. Reservoirs can be wild animals, domestic animals or even the environment (water, soil).

3.3.2 Pathogen Transmission

A pathogen can pass from a reservoir to a human through various routes: direct contact with infected animals, bites or stings from insect vectors (e.g. mosquitoes or ticks), contaminated food or water, airborne (e.g. inhalation of droplets containing viruses or bacteria from an infected person).

3.3.3 Human Infection

After transmission, the pathogen enters the human body and begins to multiply. This can occur through various portals of entry, such as the respiratory tract, gastrointestinal tract, skin, or mucous membranes.

3.3.4 Development of Infection

After infection, the pathogen begins to interact with the human immune system. Depending on the type of pathogen and the state of the immune system, symptoms of the disease may appear. Some infections can be acute, chronic, or asymptomatic. The body's resistance to infections depends on its immune system. Immunity can be innate or acquired, and its status can affect the likelihood of infection.

3.3.5 Transmission from Person to Person

Some infections can also be transmitted from person to person, which helps them spread in a population. This can happen through direct contact, airborne droplets, shared objects, or vector organisms.

4. Mechanism of Virus Formation in Body Cells

Virus formation in body cells is a complex process that depends on the interaction of the virus with cellular mechanisms. Viruses are parasites that use the mechanisms of host cells to reproduce. Let's look at the main stages of this process.

4.1 Attachment and Penetration

Viruses attach to specific receptors on the surface of host cells. After that, they penetrate the cell using endocytosis or fusion with the cell membrane.

4.2 Viral Disassembly

After penetration, the virus releases its genetic information (DNA or RNA) and protein components into the cell.

4.3 Genome Replication

The virus uses host cell machinery to replicate its genome. This can occur in the nucleus (for DNA viruses) or in the cytoplasm (for RNA

viruses).

4.4 Protein Synthesis

The viral genes are transcribed and translated into the proteins needed to form new virus particles. These proteins may include structural components (capsids) and enzymes (such as polymerases).

4.5 Assembly

New virus particles assemble in the cell. This occurs when viral proteins and genetic material come together to form new virus particles.

4.6 Cell Infection

The new viruses leave the cell to infect other cells. This can occur through the cell membrane (exocytosis) or by lysis of the cell, which leads to its death.

In a disturbed cellular environment, the mechanisms of its functioning are altered, which leads to unusual replication pathways of viruses or changes in their virulence. In such conditions, viruses can use damaged cellular mechanisms for their replication, which contributes to the spread of infections and deterioration of the host cells.

5. Intelligent Digital Clinic of AI Assistants

5.1 Intelligent Digital Assistants

Intelligent digital assistants are software that uses artificial intelligence technology to perform various tasks and assist users in their daily lives. Such assistants can work on various devices, including smartphones, computers, smart speakers, and other smart devices. The following are the key features and functions of an intelligent digital assistant:

1) Assistants can understand and process user requests in natural language, allowing them to interact with them in a convenient and intuitive manner,

2) Many digital assistants support voice commands, allowing users to control devices and get information without typing,

3) Assistants can be customized based on user preferences, remember their interests and offer personalized recommendations,

4) Digital assistants can be integrated with various services and applications, such as calendars, email clients, delivery services and many others,

5) Assistants can perform routine tasks such as reminders, scheduling meetings, sending messages and managing smart institution devices,

6) They can provide users with information on request, depending on their specialization,

7) Using machine learning, assistants can improve their responses and recommendations based on user interactions,

8) Modern digital assistants are designed with security and data protection issues in mind, giving users the ability to control what information is collected and how it is used,

9) Intelligent digital assistants can interact with each other.

Interaction between AI assistants can take various forms and for various purposes. AI assistants can work together to perform complex tasks. For example, one assistant can collect information, and another can analyze it and provide recommendations.

AI assistants can exchange data and work results to improve the quality of services provided. This can include joint access to databases and algorithms.

AI assistants can learn from each other's work, improving their algorithms and approaches to solving problems. In situations where a multifaceted approach is required, assistants can combine efforts to solve a problem more effectively, for example, in the field of medical diagnostics or data analysis.

An AI assistant can interact with several assistants at the same time, which allows for a more complete and detailed understanding of the information needed. AI assistants can interact with other software systems and platforms, which expands their functionality and improves professional experience.

These and other aspects of interaction are useful and effective in the healthcare sector. Intelligent digital assistants continue to develop, becoming more advanced and useful in medicine and everyday life. Intelligent digital clinics from AI assistants are beginning to form in medicine. To implement intelligent digital clinics, DeepSeek can be transformed into various interacting AI assistants.

5.2 Intelligent Digital Clinic of AI Assistants

The intelligent digital clinic based on interacting AI assistants is an intelligent healthcare system in which multiple digital assistants work together to provide comprehensive support to

patients and medical staff. Here is how the intelligent digital clinic functions:

1) Each AI assistant specializes in certain aspects of healthcare, such as diagnostics, record management, medical history, medication reminders, etc.

2) Assistants exchange information with each other to create a complete picture of the patient's health. For example, one assistant can provide data on symptoms, and another can process it to create a preliminary diagnosis.

3) Assistants are customized for each patient, taking into account their medical history, preferences, and individual needs. This may include medication reminders, lifestyle and dietary recommendations.

4) Assistants organize video calls with doctors, preparing the patient for the meeting, collecting the necessary data and questions for discussion.

5) Assistants analyze patient data and provide the doctor with diagnostic and treatment recommendations based on best practices and the latest research.

6) Assistants track the patient's health through wearable devices, collecting information on physical activity, blood sugar levels, and other indicators.

7) Assistants collect patient feedback on the quality of service and use this data to improve their recommendations and functions.

8) Assistants make an appointment with a doctor for a specific day and time and remind the patient about it.

All interactions between assistants and patients are protected using modern encryption technologies and compliance with privacy standards.

The intelligent digital clinic improves the quality of medical care and makes it more accessible and personalized for each patient. Patients can receive consultations from doctors remotely via video link, which is especially convenient for people with disabilities or living in remote areas.

All patient data is stored electronically, which simplifies access to information for doctors and improves coordination between different specialists.

Large amounts of data collected from various sources (e.g. test results, medical history) can be analyzed to identify trends, improve the quality of care and develop new treatment methods. Based on the collected patient information, including genetic data, individual treatment plans can be developed, which increases the effectiveness of therapy.

Appointments, insurance processing, documentation and ensuring territorial interaction are automated, which allows medical staff to focus more on the innovative development of the intelligent digital clinic. For example, using the technology of chromatin conformation in cells.

5.3 Chromatin Conformation in Cells

Every cell in your body has the same genetic sequence, but only uses some of those genes. This is what differentiates brain cells from skin cells. The three-dimensional structure of the genetic material determines which genes are accessible. Chemists at MIT have found a new way to predict these three-dimensional structures using artificial intelligence (AI) that is much faster than older methods. This new technology, called ChromoGen, can predict thousands of structures very quickly (Greg Schuette, Zhuohan Lao & Bin Zhang, 2025). It helps scientists see how the three-dimensional shape of DNA affects cell function.

A cell's function depends on which genes are accessible to it. To study this process, DNA sequences are analyzed and modeled as they fold. By quickly mapping how chromatin folds, the ChromoGen system allows scientists to compare cell types, study gene regulation, and investigate how DNA mutations affect structure. This could lead to a better understanding of diseases linked to genetic changes and open up new avenues for epigenetic research.

In the cell nucleus, DNA wraps around proteins called histones to form chromatin. This chromatin has layers of organization that allow it to fit into tiny spaces. Epigenetic modifications, such as marks on the DNA, affect how the chromatin folds and which genes are turned on or off. Standard methods map these structures by linking nearby pieces of DNA, but they are slow. ChromoGen uses deep learning to read DNA and predict how it might twist and turn in cells. It combines two parts: one that reads the DNA, and the other uses AI to model the 3D shape based on vast amounts of previous data from experiments.

Deep learning methods have made it possible to predict the chromatin conformations of individual cells directly from sequencing data.

The researchers tested ChromoGen on more than 2,000 DNA sequences and found that its predictions matched the real data. ChromoGen can even predict structures in cell types it wasn't trained on, helping compare how chromatin varies between cells and what that means for gene activity. It can also investigate how DNA mutations change chromatin structure, linking this to disease. This study opens new avenues for studying cell biology using AI-powered virtual cells (Theofanis Karaletsos et al., 2024; Wenpin Hou et al., 2024; Bunne, C., et al., 2024; Laura Thomson, 2024; Charlotte Bunne et al., 2024; Amara Angelica, 2024; Le, M., 2023; Loconte, V. et al., 2023; Dalla-Torre, H. et al., 2023; Lipman, Y. et al., 2024; Nguyen, E. et al., 2024; Roohani, Y. H., 2024; Chen, R. J. et al., 2024; Abramson, J. et al., 2024; Cesnik, A. et al., 2024; Cui, H. et al., 2024; Kraus, O. et al., 2024; Chen, Y., 2024; Krishna, R. et al., 2024; Nguyen, E. et al., 2024; Celaj, A. et al., 2023; Evgeny Bryndin, 2024; Evgeny Bryndin, 2024; Zimian Wang et al., 2024; Fei-Fei Li, 2023; Elina Stoyanova, 2024; Pavel Ivlev, 2024; Fei-Fei Li, 2025; Evgeny Bryndin, 2025; Evgeny Bryndin, 2025).

6. Conclusion

Spiritual development can help people understand that their actions have consequences. From a spiritual perspective, it is important to develop a deeper understanding and respect for nature, and to strive for harmony with the world around us (Evgeny Bryndin, 2025). This includes caring for the planet, consuming consciously, and actively participating in its protection.

Tackling the problem of waste and pollution requires a comprehensive approach, including effective waste management, protecting ecosystems, and raising public awareness of the importance of protecting nature for health. Studying how infections occur in nature helps us understand how to prevent their spread and control epidemics. This is an important area of research in epidemiology, ecology, and medicine. Studying the routes of infection helps scientists and health professionals develop disease prevention and control strategies, as well as predict and prevent outbreaks.

AI medicine helps solve the problems of detecting diseases. Today, there are many services using AI technologies in clinics and medical institutions around the world.

Babylon Health service uses AI to provide consultations on symptoms. Users can enter their symptoms, and the system provides a preliminary diagnosis and recommendations for further actions. Babylon also offers the ability to communicate with doctors via video calls.

Ada Health application uses AI to assess symptoms and provide the user with recommendations on possible diseases. The user answers the questions, after which the application analyzes the data and suggests potential causes of the disease.

Buoy Health AI platform helps users understand their symptoms and directs them to the appropriate medical specialist.

IBM Watson Health platform provides solutions for analyzing patient data and helps doctors in diagnosing and choosing the best treatment based on large volumes of medical information and scientific research.

Zebra Medical Vision company develops AI systems for analyzing medical images such as X-rays, CT and MRI to detect various diseases and health conditions of patients.

Google Health is actively working on projects related to AI in medicine, including medical image analysis and development of tools to improve disease diagnosis.

PathAI uses AI to improve disease diagnosis based on the analysis of pathological sections. PathAI systems help doctors to interpret the results more accurately.

HealthTap platform connects patients with doctors and uses AI to provide recommendations and answers to health questions.

These examples show how AI medicine is integrated into the work of clinics and medical institutions, improving the quality of service, speeding up diagnostic processes and providing a more personalized approach to each patient. As technology develops, we can expect new solutions and expansion of existing capabilities, using robotic operators with spatial intelligence (Figure 1).

Figure 1. Robotic operator

In the process of life, a person forms and develops a three-level spatial intelligence: adaptive, mental and ethical. Adaptive intelligence develops in the environment, forming a spatial adaptive ontology in memory. Mental intelligence develops through multimodal communication, learning, problem solving and decision making, forming a spatial semantic ontology in memory. Ethical intelligence develops according to ethical values, forming spatial value ontology in memory.

Ontology is used in decision-making in real time at every moment of adaptive, mental or ethical activation of person in space.

Modern technologies of artificial adaptation (visual, navigation, tactile, etc.) in the environment, generative intelligence and a virtual ethical environment make it possible to create robots with spatial intelligence as assistants for interaction in a real environment.

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Esterification of Many Drugs Causes Its Prolonged Action Due to Increase Lipid Solubility and Store in Fatty Tissues

Rezk R. Ayyad[1], Ahmed M. Mansour[2], Ahmed M. Nejm[3], Yasser Abdel Allem Hassan[4] & Ahmed R. Ayyad[5]

[1] Pharmaceutical Medicinal Chemistry Department, Faculty of Pharmacy, Al-Azhar University, Cairo, Egypt
[2] Pharmacology and Toxicology Department, Faculty of Pharmacy, Al-Azhar University, Cairo, Egypt
[3] Faculty of Pharmacy, Al-Azhar University, Cairo, Egypt
[4] Pharmaceutics and Pharmaceutical Technology Department, Faculty of Pharmacy, Delta University for Science and Technology, Gamasa, Addaqahlya, Egypt
[5] Faculty of Medicine, Asfendiyarov Kazakh National Medical University, Almaty, Kazakhstan
Correspondence: Rezk R. Ayyad, Pharmaceutical Medicinal Chemistry Department, Faculty of Pharmacy, Al-Azhar University, Cairo, Egypt.

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Abstract

The esterification process is a reaction between alcohol and acid which increases the resistance to metabolism, increases lipid solubility, and takes time to liberate the active constituent either alcohol or acid. Fluphenazine is an antipsychotic drug that is in the form of decanoate which is prolonged in its action making it take 1 month. Nandrolone decanoate, progesterone acetate, propionate and cypionate, also benzathine and penicillin procaine.

Keywords: esterification, acid, alcohol, phenothiazine, progesterone, testosterone, lipid solubility, hydrolysis

1. Introduction

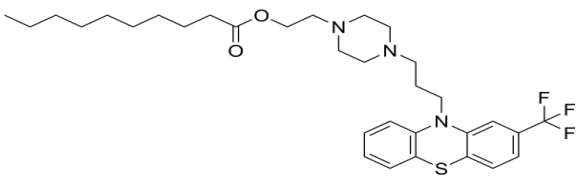
The drugs in ester forms are depot in fatty tissue and take time to hydrolysis and liberate the original drugs, for example, fluphenazine decanoate is a prolonged drug used in the treatment of schizophrenia which requires many doses each month, hence, the esterification of fluphenazine solves the problem of repeated doses.

Benzathine penicillin is a benzylpenicillin with benzathine that forms salt, and no ester but forms a complex compound which is depot in fatty tissues and released gradually to the blood.

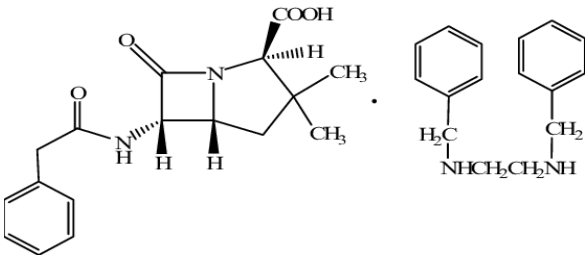
Progesterone is a female sex hormone which in ester forms acetate, propionate, and cypionate which make the progesterone prolonged in action due to storage in fatty tissues and takes a long time to hydrolysis and release the

progesterone, also testosterone is the male sex hormone in form acetate which prolonged its action. Nandrolone decanoate is a male sex hormone which has mainly anabolic activity, this ester form makes it a prolonged action and depot in fatty tissues.

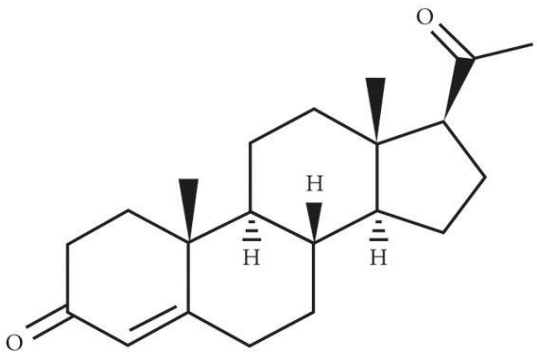
2. Chemistry and Pharmacology



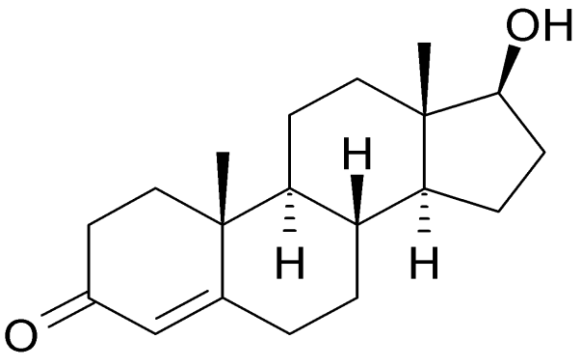
Fluphenazine is a drug used for the treatment of schizophrenia. It has a phenothiazine ring and is an ester formed from fluphenazine and decanoic acid to form fluphenazine decanoate. It is used to relieve the need for repeated injections in patients, as it is taken once per month. This esterification prolongs the action of fluphenazine.



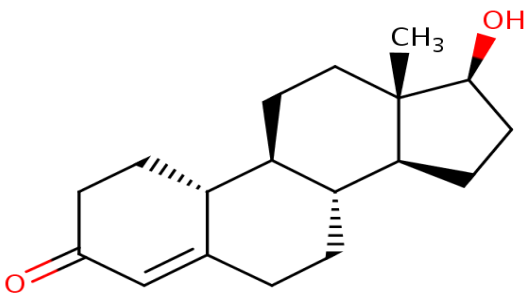
Benzathine penicillin is a salt formed from 2 mol of penicillin G and 1 mol of benzathine (N, N-dibenzyl ethylene diamine). It is not an ester, but a salt that forms a depot in the fatty tissue and is slowly hydrolyzed. It is used in the prevention of rheumatic heart fever, which arises from a streptococcal infection. Benzathine penicillin is a beta-lactam antibiotic with long-acting properties.



The esterification of progesterone with acetic acid and propionic acid form esters of progesterone which is depot in the body in the treatment of early abortion in the first months of pregnant women, hence these esters make the progesterone prolonged action in this case and in deficiency of progesterone.



Testosterone is a male sex hormone which is in ester form, where the ester is more lipid soluble than the parent testosterone, testosterone has anabolic and androgenic effects i.e., builds the muscles and increases the spermatogenic effect in males, so testosterone is used in depot form due its steroidal nucleus and its ester form.



Nandrolone is a male sex hormone, which is nor-testosterone, an endogenous hormone resulting from the metabolism of testosterone via oxidative dealkylation. Nandrolone decanoate is an ester form, which forms a depot in adipose tissue that is hydrolyzed at a slow rate and gives a prolonged action. Nandrolone is an anabolic compound more than an androgenic compound, i.e., used in muscle building.

3. Conclusion

The esterification of pharmaceutical compounds significantly enhances their therapeutic profiles by increasing lipid solubility and facilitating depot formation in fatty tissues. This process effectively prolongs the action of various drugs, such as fluphenazine decanoate, benzathine

penicillin, progesterone esters, testosterone esters, and nandrolone decanoate. By slowing the hydrolysis of these compounds, esterification reduces the frequency of administration required, thereby improving patient compliance and therapeutic outcomes.

The strategic use of esterified drugs offers distinct advantages, particularly in managing chronic conditions where long-lasting effects are essential. As demonstrated, the modified pharmacokinetics resulting from esterification not only alleviate the burden of regular dosing but also optimize the therapeutic efficacy of these agents. Future research should continue to explore the potential of esterification in developing new formulations that deliver improved pharmacological benefits while minimizing side effects.

In summary, the application of esterification in drug design represents a valuable tool in enhancing the functionality of various pharmacological agents, ultimately leading to better patient care and treatment effectiveness.

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Application of Stereotactic Body Radiation Therapy in the Local Treatment of Primary Renal Cell Carcinoma: A Review

Junming Zhu[1], Xinyi Cao[1], Ye Tian[1] & Hongbin Deng[1]

[1] Department of Oncology, Laboratory of Immunity, Inflammation & Cancer, The First Affiliated Hospital of Chongqing Medical University, Chongqing 400016, China
Correspondence: Hongbin Deng, Department of Oncology, Laboratory of Immunity, Inflammation & Cancer, The First Affiliated Hospital of Chongqing Medical University, Chongqing 400016, China.

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Abstract

Renal cell carcinoma (RCC) is one of the most common malignant tumors of the urinary system in adults, with its incidence steadily increasing, posing a significant threat to the health of elderly patients. Surgery remains the standard treatment for primary RCC; however, surgical intervention is often limited in elderly patients due to the frequent presence of multiple comorbidities. In recent years, stereotactic body radiation therapy (SBRT), with its high dose per fraction, high precision, and non-invasive nature, has been widely used for local management of primary RCC. This article reviews the application and related research of SBRT in the local treatment of primary RCC.

Keywords: stereotactic body radiation therapy, primary renal cell carcinoma, non-surgical treatment

1. Introduction

Renal cell carcinoma (RCC) is one of the most common tumors of the urinary system, with its incidence steadily increasing (TORRE L A, BRAY F, SIEGEL R L, et al., 2015). According to data from the Chinese Cancer Registry, the incidence rate of RCC in China in 2022 was about 3.13/100,000, with a total of approximately 73,700 new cases and a mortality rate of about 0.91/100,000, leading to 24,000 deaths (FUSCO V, PARISI S, D'ANDREA B, et al., 2017). It primarily affects the elderly population, with a median diagnosis age of 65 years (DENGINA N, TSIMAFEYEU I & MITIN T., 2017). The cancer-specific mortality (CSM) of RCC patients increases with age, and the CSM of patients over 80 years old may be 1.9 times higher than that of patients under 50 years old. Moreover, advanced age has a particularly adverse impact on patients with stage I RCC, as the risk of CSM may be 3.8 times higher compared to patients with other stages at the same age (SUN M, ABDOLLAH F, BIANCHI M, et al., 2011). This suggests that even early-stage RCC exhibits aggressive behavior in the elderly population. The selection and implementation of treatment strategies for elderly patients with RCC are complex and challenging. Surgery remains the standard treatment for primary RCC (DENGINA N, TSIMAFEYEU I & MITIN T.,

2017), however, advanced age and the frequent presence of comorbidities such as diabetes, hypertension, chronic kidney disease, and cardiovascular diseases, which exacerbate renal functional burden, may hinder the feasibility of anesthesia and surgery (CORREA R J M, LOUIE A V, ZAORSKY N G, et al., 2019). For patients deemed unsuitable for surgery, it is imperative to develop and validate non-surgical treatment options in prospective clinical trials.

Stereotactic Body Radiation Therapy (SBRT) is a radiation therapy technique capable of delivering high fractional doses. By utilizing high doses of radiation, it precisely targets tumor tissues while minimizing damage to surrounding normal tissues. It combines the precision of stereotactic radiosurgery (SRS) with the techniques of external beam radiation therapy (EBRT), enabling the delivery of high-dose radiation to tumors in a small number of sessions. With the continuous advancements in modern linear accelerators and precise image-guided capabilities, SBRT is rapidly being integrated into many radiation therapy departments (KOTHARI G, LOUIE A V, PRYOR D, et al., 2017), and SBRT's advantages in precise dose control and normal tissue protection have become more evident (Le Z, Liu Y, et al., 2018). Several phase II clinical trials have evaluated the effectiveness and safety of SBRT for the treatment of Primary RCC. This article provides a review of the relevant research and advancements in the application of SBRT for the local treatment of primary RCC.

2. Biological Mechanisms of SBRT in Killing RCC Cells

For a long time, RCC has been considered resistant to radiotherapy, as RCC cell lines are among the most resistant to conventional fractionated radiotherapy in vitro (LEEMAN J E., 2023). Deacon et al. classified malignant histologies into five groups based on their in vitro radiosensitivity, with RCC grouped alongside sarcomas, melanomas, and glioblastomas in the most "radioresistant" category (JD, JPM & GSG., 1984). However, a study on two human RCC cell lines (Caki-1 and A498) showed that RCC has a low α/β ratio, making it potentially more sensitive to high-dose fractionated radiotherapy, especially when the single dose is increased to 6 Gy, significantly reducing cell survival rates (NING S, TRISLER K, WESSELS B W, et al., 1997). Unlike traditional radiotherapy, which kills tumor cells by damaging DNA double strands through ionizing radiation (Feng Y, Tu W, Yu D, et al., 2023), ablative dose fractionated radiotherapy activates acidic sphingomyelinase, hydrolyzing sphingomyelin on the cell surface to generate pro-apoptotic ceramide (Liang C, Shen Y, et al., 2019). The production of ceramide sensitizes tumor endothelial cells to radiation, leading to endothelial cell apoptosis (ALI M, MOOI J, LAWRENTSCHUK N, et al., 2022). High-dose radiation can also induce vascular collapse within the endothelium, causing microvascular damage to tissues and leading to tumor cell apoptosis, which is crucial for targeting vascular malignancies such as RCC (SATHISHKUMAR S, BOYANOVSKY B, KARAKASHIAN A, et al., 2005). Recent studies have shown that SBRT can enhance the body's immune response to tumors by triggering the release of pro-inflammatory mediators, upregulating tumor-associated antigen (TAA) expression, and increasing T-cell infiltration, thereby inducing tumor inflammation (SINGH AK, WINSLOW TB, KERMANY MH, et al, 2017). Overall, high-dose fractionated radiotherapy can not only directly eliminate tumor cells to stop tumor growth but also potentially induce vascular damage and enhance anti-tumor immune responses, indirectly promoting tumor cell death. This finding provides a new approach for RCC treatment, indicating the potential application value of SBRT in RCC therapy.

3. SBRT Applied to Local Treatment of Primary RCC

3.1 SBRT Is Suitable for Patients Who Are Unable to Tolerate Surgery

Historically, primary RCC have achieved favorable treatment outcomes through surgical intervention. However, surgery is an invasive treatment option and is unsuitable for patients with bilateral renal tumors, a solitary kidney, pre-existing chronic kidney disease (CKD), or those in poor physical condition who cannot tolerate surgery (KOTHARI G, LOUIE A V, PRYOR D, et al., 2017). Currently, the National Comprehensive Cancer Network (NCCN) guidelines for kidney cancer state that "SBRT may be considered for medically inoperable patients with stage I renal cancer (Category 2B) and stage II/III renal cancer (Category 3)." Similar recommendations are also found in the guidelines of the European Association of Urology (EAU) and the European Society for

Medical Oncology (ESMO) (BE, CP, MS, et al., 2019; BöRJE L, LAURENCE A, YASMIN A, et al., 2022; JMR, ERIC J, NEERAJ A, et al., 2022). In one study, Grelier et al. (2021) reported outcomes for 23 frail primary RCC patients treated with SBRT, with a median age of 81 years. All patients were medically ineligible for surgery due to comorbidities and advanced age, and unsuitable for thermal ablation due to tumor size (>4 cm) or proximity to renal pelvic structures. After a median follow-up of 22 months, local recurrence-free survival, cancer-specific survival (CSS), and overall survival (OS) were 96%, 96%, and 83%, respectively, with no grade 3-4 toxicities. SBRT appears to be a promising alternative for treating primary RCC in frail patients.

In a 2019 meta-analysis by Correa et al. (2019), changes in renal function before and after SBRT were reported in 372 RCC patients. The mean difference in estimated glomerular filtration rate (eGFR) before and after treatment was -7.7 ml/min. Most patients had some degree of renal impairment (mild to moderate CKD) prior to SBRT, resulting in a weighted mean eGFR of 59.0 ml/min. These data suggest that SBRT may be a safe strategy even in patients with pre-existing renal impairment, offering a viable option for those unsuitable for surgical resection. In this meta-analysis, none of the 35 patients with a solitary kidney required dialysis. Another study of 7 patients with a solitary kidney reported that only 2 experienced a moderate increase in creatinine levels to 160 μmol/L, and no patients required dialysis (SVEDMAN C, KARLSSON K, RUTKOWSKA E, et al., 2008). These findings suggest that SBRT can be safely administered to patients with a solitary kidney, as renal function can be adequately preserved even without a contralateral kidney. A retrospective study involving 74 primary RCC patients found that over time after treatment, ipsilateral renal function progressively declined while contralateral renal function progressively increased. Additionally, a larger volume of unirradiated renal cortex was significantly associated with better long-term renal function (GLICKSMAN R M, CHEUNG P, KOROL R, et al., 2023). This suggests that, although many studies have provided encouraging results, further data are needed to establish safe dose limits for patients with pre-existing renal impairment. Minimizing high-dose exposure to the ipsilateral renal parenchyma is crucial to better preserve post-treatment renal function.

3.2 SBRT Is Suitable for Patients with Larger Primary Tumor Volumes (>T1b)

Partial nephrectomy, which preserves kidney function, is a viable option for T1b primary renal cell carcinoma in patients who can tolerate surgery. However, evidence for its use in T2 stage patients is limited (BE, CP, MS, et al., 2019; BöRJE L, LAURENCE A, YASMIN A, et al., 2022). For larger tumors, thermal ablation techniques such as Radiofrequency Ablation (RFA) and Cryoablation (CA) are associated with higher local recurrence rates (up to 14.3% for RFA and 23% for CA) (CAPUTO P A, ZARGAR H, RAMIREZ D, et al., 2017; PSUTKA S P, FELDMAN A S, MCDOUGAL W S, et al., 2013) and increased rates of major complications, such as bleeding (KURUP A., 2014) or patients with larger tumors, SBRT may be a favorable alternative, offering advantages such as non-invasive ablation, the ability to treat larger tumors, and excellent local control rates (LCR) with low toxicity. In a retrospective report from the International Radiosurgery Oncology Consortium for Kidney (IROCK), Siva et al. presented outcomes of SBRT in 95 patients with T1b renal cancer (median tumor diameter: 4.9 cm). With a median follow-up of 2.7 years, the local treatment failure rate was 2.9%, and the 4-year overall survival (OS), and progression-free survival (PFS) rates were 69.2% and 64.9%, with no grade 3-5 treatment-related adverse events (AEs) were reported (SIVA S, CORREA R J M, WARNER A, et al., 2020). Another retrospective study of ≥T1b primary renal cancer patients treated with MRI-guided SBRT included 36 patients with a median tumor size of 5.6 cm, who received 40 Gy in five fractions over two weeks. At a median follow-up of 16.4 months, the 1-year LCR, OS, and PFS rates were 95.2%, 91.2%, and 91%, respectively (TETAR S U, BOHOUDI O, SENAN S, et al., 2020). Additionally, a prospective, multi-institutional Phase II study (NCT02613819) by the Trans-Tasman Radiation Oncology Group (TROG) and the Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP) is ongoing, involving 70 patients with primary RCC. The study has completed full accrual, and the results are highly anticipated (SIVA S, CHESSON B, BRESSEL M, et al., 2018).

3.3 SBRT for Primary RCC with Inferior Vena Cava Tumor Thrombus

Primary renal cell carcinoma can form tumor thrombi within the renal vein, extending into the inferior vena cava (IVC) in approximately 4-10% of patients, resulting in IVC tumor thrombus (IVC-TT), which may even reach the right atrium. IVC-TT can lead to severe complications such as pulmonary embolism or Budd-Chiari syndrome. The only potentially curative treatment option for IVC-TT is nephrectomy. However, this procedure carries a risk of severe surgical complications, including mortality, and a high risk of tumor recurrence (HADDAD A Q, WOOD C G, ABEL E J, et al., 2014). Neoadjuvant SBRT has been explored with the aim of improving disease control in RCC patients with IVC-TT. Margulis et al. (2021) reported preliminary results from the safety run-in phase of an ongoing Phase II trial (NCT02473536) investigating neoadjuvant SBRT for newly diagnosed RCC tumor thrombi, involving 6 patients. All patients received SBRT (40 Gy in 5 fractions) targeting the IVC tumor thrombus, followed by surgery. A total of 81 adverse events were reported within 90 days post-surgery: 4% were grade 3, with no grade 4 or 5 events. At a median follow-up of 24 months, all patients were alive. Neoadjuvant SBRT resulted in a reduction in Ki-67 and an increase in PD-L1 expression within the IVC-TT. In patients without progressive disease, inflammatory cytokines and autoantibody titers reflecting an improved host immune state were observed. The results of the Phase I trial demonstrate that neoadjuvant SBRT for primary RCC with IVC-TT is feasible and safe, and the ongoing Phase II trial's efficacy evaluation is highly anticipated.

4. Exploration of Optimal Fractionation Doses for SBRT

In SBRT for early-stage non-small cell lung cancer (NSCLC), regimens with a BED_{10} ≥100 Gy have been shown to improve local control and overall survival (ONISHI H, ARAKI T, SHIRATO H, et al., 2004). However, no consensus has been reached on the optimal dose fractionation for renal SBRT. In a systematic review and meta-analysis reported by Correa et al. (2019), various dose fractionation schemes were used for primary renal cell carcinoma across the included studies. The most common regimens were single-fraction 26 Gy and five-fraction 40 Gy. Reported local failures often occurred in the low-dose groups or in cases where tumor dose was limited by adjacent tissue constraints. A retrospective study of 74 primary RCC patients treated with SBRT primarily used 35 Gy in 5 fractions (BED_{10} 59.5 Gy) or 40 Gy in 5 fractions (BED_{10} 72 Gy). The study found that when the mean PTV (planning target volume) dose was ≥40 Gy, over 95% of patients achieved local tumor control (GLICKSMAN R M, CHEUNG P, KOROL R, et al., 2023). Grubb et al. (2021), PONSKY L, LOSS, ZHANG Y, et al. (2015) conducted a prospective dose-escalation study of SABR in 11 primary RCC patients. Initial SBRT doses of 48 Gy in 4 fractions (BED_{10} 105.6 Gy) were well-tolerated, prompting escalation to 60 Gy in 3 fractions (BED_{10} 124.8–180 Gy). At a median follow-up of 34.3 months, the 3-year local control rate was 90%, with no dose-limiting toxicities (DLTs). Acute toxicities were limited to grade 1 fatigue and nausea, while late toxicities occurred at rates of 18.1% and 9.1%, respectively.

Currently, extensive prospective data are still needed to determine the maximum safe dose levels for optimizing local control rates while minimizing toxicity. Until longer follow-up and more prospective studies are available, clinical practice should adhere to the IROCK consensus statement, which recommends single-fraction doses of 25-26 Gy, three-fraction doses of 35-45 Gy, and five-fraction doses of 40-50 Gy (SHANKAR S, J E R, LEE P, et al., 2016).

5. Future Directions

Current studies have demonstrated high long-term local control rates with SBRT for primary renal cell carcinoma. However, longer follow-up data are still needed to evaluate its impact on overall survival. Future efforts should focus on long-term follow-up and establishing comprehensive systems to promptly identify and manage potential late toxicities. And the optimal dose fractionation scheme for renal SBRT has not yet reached a consensus. Future research should continue to explore more effective dose fractionation strategies to improve efficacy and reduce toxicity. Thermal ablation techniques and surgical intervention, are also recommended by the NCCN guidelines for the local treatment of renal cell carcinoma. Future randomized controlled trials are needed to compare the safety and efficacy of SBRT with these treatment modalities, further clarifying which RCC patients may benefit most from SBRT to develop more personalized treatment strategies.

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Application and Investigation of Peer Teaching Model in Clinical Practice Skills Teaching

Qian Li[1,2], Maoling Zhu[1,2], Shibo Zhao[1,2], Zhangzhi Li[1,2], Qingqing Nong[1,2], Huihui Hou[1,2], Huaye Lao[1,2], Chunda Zhang[1,2] & Yi Liang[1,2]

[1] The Second People's Hospital of Nanning, Nanning, Guangxi, China
[2] The Third Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi, China
Correspondence: Yi Liang, The Second People's Hospital of Nanning, Nanning, Guangxi, China; The Third Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi, China.

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Abstract

Peer practice teaching is a kind of student-oriented teaching method, which refers to the teaching of clinical skills, so that students can learn and practice independently, teach each other, correct each other, and think and exchange and discuss within the team, and no longer just directly inculcate the content of the study to the students, but provide students with problematic situations, some clinical cases and problems in the course, so that students can actively think, independently explore, conducting practical activities on their own The application of peer education teaching in the reform of clinical skills teaching promotes interns' independent learning and exploration skills, strengthens memory and effectively reinforces skills. The peer teaching model is rooted in the clinical skills teaching reform model, and its advantages and limitations in clinical skills teaching are studied. The study finds that the peer teaching mode breaks the traditional teaching too single duck teaching situation, and greatly cultivates the medical students' independent thinking and exploring problem ability. Peer education exists for the cultivation of students' ability to explore and think, and the self-exploration, self-answer, and self-extension classroom can enhance undergraduates' thinking ability and make students change from passive acceptance of knowledge to independent demand for knowledge, which can play an indispensable role in cultivating the clinical thinking of interns and promoting the development of clinical practice-oriented talents.

Keywords: peer education, clinical skills, teaching methods, teaching reform, clinical teaching

1. Introduction

Peer education, also known as partner education, is a form of education in which people with certain similar characteristics (e.g., age, background, educational stage, etc.) learn together and influence each other so as to achieve common learning goals (Nie Xiangyi & Wang Runian, 2024). Peer education for college students refers to educators give full play to the role of college students' partners (Fan Lu & Zhai Ziyi, 2024), planned and purposeful organization of college students to teach each other learning, life, work and other aspects of experience, timely exchange of ideas, psychological exchanges and communication,

guiding partners to do their best to give each other spiritual encouragement and learning to help each other, so that each other to fully experience the love and care of the partners around them, so as to see the wise and clear, and to achieve complementary advantages, mutual promotion, and to achieve the goal of mutual improvement, and to achieve the goal of common learning. Realize the complementary advantages, mutual promotion, common growth of the educational approach (Wang Ying et al., 2024; HOU Huihui, TANG Zhenkun & LI Qian, 2023). Because of the commonality of age, interest, attitude, values, social status and other aspects of the university student group, they are often able to listen to or adopt the opinions and suggestions of their peers.

Clinical skills are medical students must master professional knowledge and technology, belong to the practical professional application, but for a long time our country's medical school more one-sided emphasis on teachers, books, classroom-centered, teachers one-way lecturing students' passive acceptance, the lack of interaction between teachers and students, students lack of learning enthusiasm and initiative (Li Liu-Lan & Zhou Li-Jun, 2024; Li Panyi et al., 2024; YANG Hui et al., 2024). Peer teaching mode is in the same undergraduate medical students in the internship phase of standardized training, after passing the examination to all students to carry out skills teaching, respectively, the teaching content in the group to carry out discussion, demonstration, teaching, and ultimately by the teacher unified organization of the assessment, and in the post-course summaries and theoretical supplements. Peer teaching mode defines students as the main implementer of classroom teaching, through the bond and connection between friends and classmates, based on the peer relationship as the main carrier of the teaching carried out by classmates with classmates, friends with friends to continuously strengthen the memory, effectively promote the continuous deepening of knowledge, so that students independently learn the concepts and think about the principle of self-exploration, self-answers, self-extension, so as to achieve the interns wholeheartedly devoted to the classroom. The common traditional teaching is the teacher teaching textbook content knowledge, students listen to the class, passive acceptance of knowledge, teachers and students in the classroom often lack of interaction and communication, and the traditional teaching method of the classroom to the teacher to explain, students end of the textbook to listen to, will inevitably result in the passivity of the students to learn and difficult to wholeheartedly engaged. Peer teaching mode is the sublimation of the traditional teaching method, is a form of active acquisition of knowledge, cultivate the ability to think (LI XING et al., 2024), can enhance the ability of students' comprehensive practice, exercise students' clinical thinking ability, improve students' interest in learning, so that the quality of teaching can be further improved, and compared with the traditional mode of instruction has significant advantages.

2. The Necessity of Implementing the Peer Teaching Model in Teaching Clinical Skills

Clinical skills are a necessary and directly determine the watershed of the high and low level of the comprehensive level of clinicians in the teaching of clinical medical disciplines, involving the whole, individual, multi-systems, multi-organs, multi-dimensional disciplines, and the clinical disease is also complex and variable (Li Xiao et al., 2024). Lack of thinking about copying knowledge from textbooks, and one-dimensional filler lectures gradually show a series of problems, and lack of thinking about the disease is very difficult to think and judge. Then how to make undergraduates in the case of solid theoretical knowledge, but also have a strong more clinical analysis ability and application of practical ability, to meet the needs of contemporary society for medical personnel, is the main goal of the current era of development of teaching reform, but also clinical skills teaching on the important issues faced. Peer education through the students to teach the basic theory and practice of teaching, by the communication between the group practice, skills demonstration, by the students to discuss with each other to find the answer, the groups summarize the answer to the question, the teacher to summarize, correct, deepen, summarize and so on. This kind of learning, teaching, research are by the students self-study, self-discovery, self-thinking, self-solution, with the students as the main body, the teacher as an auxiliary, so that the teaching from the one-way filler to the students' independent search for knowledge mode, the teacher demonstrates the traditional classroom into a peer classroom

students actively participate in the textbook of the theoretical knowledge of the textbook to learn and utilize the clinical skills skillful use (Guo Zhenlei, 2024). Subconsciously cultivate clinical thinking ability, and lay the foundation for becoming a clinician with solid theory and pure skills in the future.

3. The Use of Peer Education Model in Teaching Clinical Skills

3.1 Peer Teaching Classroom Design

Some scholars advocate that teaching and learning activities should combine learning knowledge and exploring knowledge, so that students can develop their own reasoning thinking skills through the process of discovering concepts by themselves. The classroom design of the peer teaching model is as follows.

3.1.1 Starting with Interest and Seeking Knowledge

Peer teaching mode should be proposed from the students' interest in the problem, simulating the clinical really case, for example: in the clinical skills teaching, the real clinical cases as an entry point, through the changes in the condition to carry out the corresponding skills operation, the students in the interest of the with the validation of self-governance to produce a strong problem-solving motivation, which is conducive to the students to explore the problem and discover the problem.

3.1.2 Teaching and Practicing the Foundations of Reasoning

The leader of each team is responsible for recording and organizing the problems mentioned by the students in the team, carrying out discussions and exchanges within the group, and helping the team members to categorize and analyze the existing problems. Teachers guide students to combine textbook knowledge with clinical case knowledge, and then finally put forward a variety of assumptions, guiding students to think out of the box. Teachers should make a good plan for the lesson before the lesson, and make a plan for the questions and solutions that students may ask during the lesson. In the clinical time teaching, teachers can give students a simple theoretical knowledge to pave the way in advance, so that students can master a simple theoretical basis for the upcoming skills practice teaching, on this basis to introduce clinical cases, ask students to put forward their own diagnosis of the case, to guide the students to think and ask questions, summarize the characteristics of the case with the knowledge learned in the classroom, put forward the basis for diagnosis and diagnostic and treatment plan, leading to the main skills operation. The students will be divided into 6-8 groups. Divide all students into 6-8 groups, each group of 6-8 people, the clinical case by group distributed to students, let students discuss by group, require each student to actively participate in the group's case discussion, encourage each student to put forward their own questions, the group began to practice skills teaching and discussion, the group collects the problem of the group first in the group students self-discussion, each other to answer members of the problem to seek answers, and finally classes in the comprehensive question to collect more questions related to the case, the questions will be synthesized by the teacher to summarize and organize, to answer the students related questions, and in-depth explanation of the pathological mechanisms and practical skills points.

3.1.3 Synthesize Critiques to Encourage Skepticism

Peer education emphasizes process, and the teaching process involves 3 processes that occur almost simultaneously: acquisition of new knowledge, conversion, and evaluation. Therefore, classroom performance is recorded and grades are evaluated during the teaching process. Teachers should actively encourage students to think and explore in the classroom, guide students to actively explore the problem, actively acquire knowledge of the problem and judge the correctness of knowledge. In the answer to the question, the teacher should not just deny the students' wrong answers, but should understand the origin of the students' answers and correct them. To actively encourage students to ask questions.

3.2 Limitations of Peer Education in Teaching Clinical Skills

First of all, the peer teaching mode, as a new type of teaching method, mainly relies on students' subjective initiative and pays more attention to students' independent learning, which is usually based on students' independent inquiry and mutual cooperation, so that students' cognition, motivation, and behavior can be effectively brought into play. But the peer

education model often exaggerates students' learning ability, ignores the importance of basic knowledge learning, and neglects the fact that the in-production process of knowledge is not the production process of knowledge (MU Rongrong et al., 2024). And in clinical practice, the variety of diseases, knowledge is complicated, if ignored to the students' knowledge of the basic diseases, then let the students independently explore that is also not any meaning. Secondly, the peer teaching mode is time-consuming, the teacher from the explanation of the basic knowledge, to the group within the exploration, practice, discussion, answer, and then to the teacher's final summary, the peer teaching mode in a short period of time to the students to teach a certain amount of knowledge and skills still need to be further optimized in the proportion of classroom time allocation.

4. The Significance of Peer Education in Teaching Clinical Skills

4.1 Facilitates the Stimulation of Students' Clinical Thinking

In the undergraduate textbook is a single type of disease, a single disease to write the mechanism of the disease, clinical manifestations and treatment, and the traditional fill-in-the-blank teaching, the students' thinking will be fixed with how to diagnose, treat, and intervene from the clinical manifestations, which will lead to the establishment of the students' cognitive knowledge of the disease is too one-sided, and when the same skills are applied to other diseases, the students are mostly unable to apply the same skills in the first time. When the same skill is applied to other diseases, students are mostly unable to utilize it flexibly in the first place. The peer teaching model combines clinical cases with textbook materials to explore and discover the connection, identification, symptoms, treatment and regression of diseases from real cases, which can strengthen the attributes of skills and advance students' knowledge of diseases from a single disease to a class of symptoms and signs. The use of the peer teaching model in clinical skills teaching does not mean that students get the concept or manifestation of a certain disease from the teacher's explanation, but in the clinical case study situation organized by the teacher, through the students' own exploration, the mutual correction of errors among classmates and the sharing of experience to link the changes of the disease with clinical skills, to find the differences in the whole and to seek unity in the differences (LIN Hongcheng et al., 2024). Peer education enables students to acquire knowledge in a way that makes their minds personally accessible, and the discovery method of teaching is an embodiment of demonstrating students' mental thinking and promoting students' acquisition of knowledge while stimulating clinical thinking.

4.2 Facilitate the Development of Students' Intrinsic Motivation for Self-Motivation

Intrinsic motivation is the motivation of human beings due to the interest in the thing itself; intrinsic motivation is the need for no other factors to interfere or for the fear of punishment to keep the action directed toward the goal. It is simply because the action itself is a motivation. In traditional fill-in-the-blank teaching, the inconsistency between the content of traditional skills teaching and the students' intellectual curiosity about the focus of disease diagnosis and treatment has resulted in a "dissonance" between motivation and interest, making it extremely difficult to stimulate the students' cognitive interest in the disease itself and their desire to learn. The use of peer teaching mode, in the content from the teaching objectives, in the method of peer initiative to seek knowledge, from the life of the clinical case material and a variety of ways to present, in a lively way so that students are eager to learn about a certain skill in clinical practice, indications, contraindications, and how to maintain the treatment, in-depth investigation of the disease healing and regression, arousing the students a strong curiosity to promote the discussion of the topic of the degree of the group. Heat, which will form a further desire to understand the cognitive exploration of the key points of the operation of the skills, fully mobilize the internal motivation of students to learn. When students are recognized in internal motivation, a strong sense of satisfaction will be generated to induce a new round of students to generate learning expectations (Zhu B, Feng L & Wu XL, 2024). Learning motivation must be based on interest and innovation. However, it is worth noting that teachers should pay attention to guiding students' attributional tendency towards skill manipulation so that they can find out the correct way of attributing skill manipulation and avoid the feeling of student helplessness caused by too much difficulty and students' inability to

start. Appropriate classroom exploration competitions will help to increase students' interest and perseverance in overcoming difficulties, and correct evaluation and rewards will be given so as to consolidate students' motivation to learn.

4.3 Facilitate Students to Improve Their Problem-Solving Skills, Exploration Skills

Peer teaching mode in clinical skills teaching to solve the problem of the presentation of students and teachers put forward a great deal of space for reflection, skills teaching is not like the theoretical teaching in the school of a single disease exposition, but more comprehensive, challenging. Diseases do not simply stay in the process of "how to happen, what performance, how to treat", but in the process of disease development will have what complications, and treatment will encounter a variety of problems. For example: how to prevent, how to delay, how to regression, etc., and so on is a problem in front of the textbooks and clinical a hurdle, but in the crossing of this hurdle at the same time, the students will find and solve problems to improve and exercise the ability. Peer teaching mode in the use of clinical skills teaching so that students in the clinical practice and the textbook can be effectively connected, and in the process of problem solving, feel different people, different ways of thinking, different ways of solving the same problem due to the different points of observation of each student, is that there can be countless different ways of solving the problem (ZHANG Huiqun et al., 2023). Let them compare the advantages and disadvantages of each solution while experiencing and summarize their own problem-solving strategies.

4.4 Discovering the Results of Learning Facilitates the Retention of Students' Memories

The memories that people keep in their minds are selective, and if the memories appear only for a certain purpose, once the purpose is realized, the memories of the changed purpose will usually be forgotten immediately. In traditional practical teaching, if students are only required to imitate the process of the textbook content of the assessment tasks, then when the assessment is passed, the basic knowledge of the skills and the operation of the main points will be naturally forgotten over time. To retain knowledge for a long period of time and to enable this knowledge to enter the long-term memory system, students need to think about how to make this learning content enter the long-term memory system of the brain, and also consider how to facilitate the retrieval of knowledge afterward. Incorporating the concept of peer education into it allows students to communicate, discuss, and express their opinions when they have complementary views, all of which are conducive to the retention of students' memories and deepen the memory nodes. The peer education model requires students to fully mobilize and think about the knowledge they have learned, use the knowledge in their original memory to answer questions, use the knowledge in the textbook to supplement their own, and constantly review and link the knowledge to enhance their memory. Memory formation is selective. New information is encoded into the memory system, and its retention time varies according to the degree of processing. In the process of memory formation, people encode into the memory system what they consider important and forget what is less important. Just as in the learning process of internal science, if one learns with questions and purpose beforehand, the effect must be more profound and long-lasting than if one blindly listens to the teacher's explanations and listens aimlessly to the lectures (Xu Na, Yang YF & Fu ZS, 2023). For example, when students look through a disease, leaving a general impression of the disease in their minds, if they explore with questions, they will easily find out the key content of the disease, review the identification of previously learned diseases, to find out the differences, so it will be easier to remember the skill indications for the operation of the main points, but also review the content of the other diseases, which is conducive to the retention of memory of knowledge.

5. Conclusion

At present, the rapid development of medical technology, and China's requirements for new medical personnel is also increasing, which requires clinical skills teaching must be high standards and strict requirements. However, examining the current status quo of clinical medical teaching, it is found that there are many shortcomings, such as the old teaching mode cannot keep up with the teaching requirements, the quality of teaching is uneven, the teaching content cannot fully meet the needs of practice, clinical needs, and students lack of basic skills training. Against the background of the

imbalance between the requirements and the actual situation, the first step we have to take should be to change the teaching mode. "Ducking teaching" is a static view of teaching that people criticize and try to change (Zhou Lingwei, Lu Chen & Nie Wei, 2022). The peer teaching model breaks the situation of duckling teaching in statistics, and forms a reflective classroom with one student as the theme and a team as the unit, with self-exploration, self-answer, self-extension, and mutual promotion within the team, which greatly cultivates the ability of undergraduate medical students to think independently and explore the problems (Chen Tingting & Deng Wenwen, 2022). The peer education model exists for the cultivation of students' exploration and thinking ability of clinical practice skills, which can enhance the clinical thinking ability of interns, and make students change the pattern of passive acceptance of knowledge into the teaching of independent demand for knowledge, which can play an indispensable role in cultivating undergraduates in medicine's clinical thinking, promoting clinical skills as well as advancing the development of clinical practice-oriented talents.

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Effectiveness of CBT vs. Pharmacotherapy for Depression in Male vs. Female Chinese University Students

Qianyu Zhou[1], Lei Zhang[1] & Weizhong Ma[1]

[1] Fujian Medical University, Fuzhou, China
Correspondence: Qianyu Zhou, Fujian Medical University, Fuzhou, China.

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Abstract

Depression among university students in China has become a growing concern, with Cognitive Behavioral Therapy (CBT) and pharmacotherapy serving as the primary treatment modalities. However, differences in gender-based responses to these treatments highlight the need for personalized approaches to mental health care. This study examines the comparative effectiveness of CBT and pharmacotherapy among male and female Chinese university students, considering variations in symptom presentation, treatment adherence, and therapeutic outcomes. Findings indicate that male students generally respond better to structured, goal-oriented CBT interventions, while female students show greater improvement in therapies incorporating emotional regulation and interpersonal connection. Pharmacotherapy effectiveness also varies, with males experiencing higher rates of medication-induced fatigue and emotional blunting, whereas females are more affected by hormonal fluctuations and weight gain. Additionally, stigma remains a significant barrier, particularly for male students, who are less likely to seek therapy due to societal expectations regarding emotional resilience. This study emphasizes the importance of personalized mental health interventions that consider gender-based psychological and biological differences. Universities should adopt flexible treatment models, integrate digital mental health platforms, and promote blended care strategies that combine CBT, pharmacotherapy, and culturally informed approaches. Expanding mental health education, improving accessibility to therapy, and reducing stigma will be crucial in optimizing treatment outcomes for Chinese university students facing depression.

Keywords: depression, cognitive behavioral therapy, pharmacotherapy, university students, gender differences

1. Introduction

Depression is a major public health concern among Chinese university students, with increasing prevalence due to academic stress, career uncertainty, and social pressures. A 2022 report by the Chinese Association for Mental Health indicated that approximately 30% of university students in China exhibit depressive symptoms, with female students being 1.8 times more likely to report clinical depression than their male counterparts. The competitive nature of higher education in China exacerbates these

issues, with 70% of students citing academic pressure as a primary stressor contributing to emotional distress (China Youth Mental Health Report, 2021).

CBT and pharmacotherapy are the two primary treatment approaches for depression. CBT has been shown to be effective in 60-70% of patients with mild to moderate depression, according to a 2021 meta-analysis conducted by Peking University. Meanwhile, SSRIs demonstrate a response rate of 50-60% within the first six weeks of treatment, but relapse rates are higher compared to CBT alone. The differences in effectiveness between these treatments are particularly relevant in the context of gender differences, where females tend to respond better to therapy-based interventions, while males exhibit greater adherence to pharmacological treatments. Given the stigma surrounding mental health care in China, only 25% of students diagnosed with depression actively seek professional help (National Health Commission, 2022), making it critical to understand how treatment options align with individual and gender-specific needs.

2. Psychological and Biological Factors in Depression Among University Students

The psychological factors contributing to depression among Chinese university students include maladaptive cognitive styles, social stressors, and coping mechanisms. A 2021 survey of 10,000 university students across Beijing, Shanghai, and Guangzhou found that 65% of students experiencing depression engaged in rumination, a repetitive negative thinking pattern strongly correlated with persistent depressive episodes. Female students demonstrated higher levels of emotional dysregulation and self-blame, whereas male students were more likely to exhibit avoidant coping behaviors, including substance use and social withdrawal.

Biologically, depression is influenced by neurotransmitter imbalances, hormonal fluctuations, and genetic predisposition. Serotonin dysregulation is observed in 75% of individuals diagnosed with depression, making SSRIs the first-line pharmacological treatment (China National Psychiatry Review, 2022). Hormonal influences contribute to gender disparities, with estrogen playing a role in serotonin transmission, leading to higher depression prevalence in females, particularly during puberty and reproductive cycles. In contrast, testosterone has been found to have mood-stabilizing effects, offering some protective benefits for males. A longitudinal study conducted at Fudan University in 2021 found that genetic predisposition plays a significant role, with individuals having a family history of depression being 2.5 times more likely to develop depressive symptoms during their university years. These biological and psychological distinctions suggest that treatment effectiveness may vary between genders, reinforcing the need for personalized intervention strategies.

3. Overview of CBT and Pharmacotherapy in Depression Treatment

CBT and pharmacotherapy offer distinct advantages in treating depression, with their effectiveness varying based on symptom severity, individual cognitive styles, and biological responses. A 2022 meta-analysis by the Chinese Psychological Association found that CBT alone leads to remission in 65% of individuals with mild to moderate depression, while pharmacotherapy alone has a remission rate of 55%. When combined, remission rates increase to 75%, particularly in individuals with recurrent depressive episodes.

CBT is particularly effective in preventing relapse, as it equips patients with long-term cognitive restructuring strategies. A 2021 study conducted at Tsinghua University followed 500 students undergoing CBT and found that only 22% experienced a relapse within two years, compared to 45% of those treated with medication alone. Pharmacotherapy, however, remains the preferred treatment for moderate to severe depression, with 60% of patients showing symptom improvement within six weeks of SSRI treatment (Shanghai Mental Health Center, 2021).

Gender differences influence treatment outcomes. Female students tend to engage more effectively with CBT, as their coping mechanisms align with cognitive restructuring techniques. In contrast, male students show greater adherence to pharmacotherapy, as it requires less emotional engagement and self-reflection. A study from Peking University's School of Psychiatry (2022) found that 70% of female students preferred therapy-based interventions, whereas 65% of male students showed better adherence to pharmacotherapy

regimens.

Despite its proven effectiveness, CBT remains underutilized in China due to the shortage of mental health professionals, with only 1.7 licensed psychologists per 100,000 people (National Health Commission, 2022). As a result, pharmacotherapy is more widely accessible, though it does not address underlying cognitive distortions, leading to higher relapse rates when medication is discontinued. These disparities highlight the importance of integrating psychotherapy and pharmacological treatment in university mental health programs to ensure students receive comprehensive, gender-sensitive care.

4. Gender Differences in Treatment Response and Effectiveness

Gender differences in the treatment response to depression have been widely documented, with significant implications for the effectiveness of cognitive behavioral therapy (CBT) and pharmacotherapy. Biological, psychological, and sociocultural factors contribute to distinct symptom presentations, treatment adherence, and therapeutic outcomes between male and female university students. While both treatments offer benefits, their impact varies based on gender-specific cognitive styles, emotional regulation patterns, and physiological responses to medication. Understanding these differences is crucial for developing personalized treatment strategies that optimize mental health interventions in Chinese universities.

4.1 Variations in Symptom Presentation and Diagnosis

Depression manifests differently in males and females, often leading to delayed diagnosis, underdiagnosis, or misdiagnosis in male students. Women tend to exhibit internalized symptoms, such as persistent sadness, excessive guilt, self-doubt, and social withdrawal, which fit conventional diagnostic criteria. These emotional expressions make depression more easily recognizable in female students, leading to higher treatment rates. In contrast, male students often externalize their distress, displaying anger, irritability, impulsive behavior, substance use, and increased risk-taking, which can lead to misclassification as behavioral disorders rather than depression.

The differences in symptom expression impact treatment-seeking behaviors, with men less likely to acknowledge emotional distress due to societal expectations of masculinity. Many male students in China experience cultural stigma surrounding mental health, believing that seeking psychological help signifies weakness or a lack of self-control. This stigma delays early intervention and results in lower engagement with psychotherapy and psychiatric services. A study conducted at Tsinghua University (2022) found that female students were 40% more likely than male students to seek psychological counseling, highlighting the gender gap in mental health service utilization.

Moreover, male students often present somatic symptoms—such as headaches, digestive problems, or chronic fatigue—rather than explicitly reporting emotional distress. This can lead healthcare providers to focus on physical health concerns, overlooking underlying mental health conditions. A 2021 survey from the Shanghai Mental Health Center revealed that male students were 30% more likely than female students to be initially misdiagnosed with a physical ailment before receiving a depression diagnosis.

4.2 Cognitive and Emotional Processing Differences

Cognitive and emotional regulation mechanisms also differ between genders, shaping treatment responses to both psychotherapy and medication. Female students tend to ruminate, meaning they repeatedly replay negative thoughts and emotions, which prolongs depressive episodes but also makes them more receptive to cognitive restructuring techniques used in CBT. This pattern aligns well with the therapeutic approach of identifying and modifying dysfunctional thought processes, allowing for higher engagement and long-term symptom improvement in female patients.

Male students, on the other hand, favor avoidance-based coping mechanisms, such as distraction, denial, or externalized behaviors (e.g., excessive gaming, substance use, or social withdrawal). While these strategies provide temporary relief from distress, they make CBT's introspective and emotion-focused techniques more difficult for men to engage with. Research conducted at Peking University (2022) found that male students were 50% more likely to disengage from therapy prematurely if sessions relied heavily on emotional self-exploration rather than action-oriented problem-solving.

Gender differences in stress reactivity also

influence treatment outcomes. Studies have shown that women experience greater activation of the hypothalamic-pituitary-adrenal (HPA) axis, leading to heightened emotional sensitivity to stress. This makes CBT an effective intervention, as cognitive restructuring and relaxation strategies help regulate emotional responses. In contrast, men exhibit lower emotional reactivity but higher physiological responses to stress, such as elevated heart rate and blood pressure, making behavioral activation and structured interventions more suitable for long-term engagement.

4.3 Medication Response and Side Effects in Males vs. Females

Gender differences in hormonal activity, metabolism, and neurochemistry lead to varying responses to antidepressant medication. Women, particularly those of reproductive age, experience estrogen-related fluctuations in serotonin levels, which influence the effectiveness of selective serotonin reuptake inhibitors (SSRIs), the most commonly prescribed antidepressants. Studies suggest that women respond more quickly to SSRIs but also experience more severe side effects, such as nausea, dizziness, weight gain, and emotional blunting.

Male students, however, metabolize antidepressants at a faster rate, requiring higher dosages for the same therapeutic effect. Despite this, they also report lower adherence due to side effects such as reduced libido, fatigue, and increased appetite. A study published by the Chinese National Institute of Mental Health (2021) found that men were twice as likely as women to discontinue antidepressants within the first six weeks due to perceived ineffectiveness or unwanted side effects.

Additionally, gender differences in dopaminergic activity influence motivation and reward processing, affecting treatment engagement. Men often report lower emotional responsiveness to SSRIs, leading to higher discontinuation rates due to the blunted emotional effect of long-term medication use. This suggests that alternative treatments, such as serotonin-norepinephrine reuptake inhibitors (SNRIs) or dopamine-based medications, may be more suitable for certain male patients.

4.4 CBT Engagement and Therapy Outcomes by Gender

While CBT remains a gold-standard treatment for depression, gender disparities in engagement and perceived effectiveness affect outcomes. Female students are more likely to complete full therapy sessions, as talk-based interventions align with their communication style and emotional processing patterns. They also engage more consistently in therapy homework, such as journaling, cognitive restructuring exercises, and mindfulness techniques, which contribute to greater long-term symptom reduction.

Conversely, male students struggle with the introspective nature of CBT, making them less likely to commit to therapy long-term. A 2022 study from the University of Hong Kong found that men were 60% more likely to drop out of CBT-based treatment within the first five sessions, citing discomfort with verbalizing emotions and a preference for action-oriented solutions.

To improve CBT's effectiveness for male students, mental health professionals have experimented with structured, goal-oriented adaptations, including:

- Behavioral Activation Therapy (BAT): Encouraging engagement in physical activities and structured routines to counteract inactivity associated with depression.
- Solution-Focused Therapy (SFT): Shifting focus from past emotional experiences to present problem-solving, which is often more engaging for male students.
- Group CBT for Men: Providing peer-based support environments, which reduce stigma and encourage open discussion in a less formal setting.

Both gender-adapted CBT and personalized pharmacotherapy regimens could improve treatment outcomes, ensuring that students receive tailored mental health support suited to their specific cognitive and emotional needs.

5. Comparative Analysis of CBT and Pharmacotherapy Outcomes

Cognitive Behavioral Therapy (CBT) and pharmacotherapy are the two most commonly used treatments for depression among university students, each with its own advantages and limitations. The effectiveness of these interventions depends on factors such as treatment duration, patient adherence, symptom

severity, and individual psychological and biological differences. In Chinese university settings, where mental health awareness is increasing but stigma still exists, understanding the short-term and long-term efficacy of CBT and pharmacotherapy, as well as student preferences and adherence behaviors, is essential for optimizing treatment approaches.

5.1 Short-Term vs. Long-Term Treatment Efficacy

In the short term, pharmacotherapy often provides faster symptom relief compared to CBT, particularly in cases of moderate to severe depression. Antidepressants, such as Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs), begin to take effect within 2 to 4 weeks, with peak effectiveness typically observed around 6 to 8 weeks. This rapid reduction in depressive symptoms makes pharmacotherapy particularly useful for students experiencing severe distress that interferes with academic performance and daily functioning.

CBT, on the other hand, requires a longer time to show significant improvements, usually over 10 to 16 sessions, which typically spans 3 to 4 months. However, CBT provides sustained benefits beyond symptom relief, as it equips students with coping skills, cognitive restructuring techniques, and emotion regulation strategies that prevent relapse. Research conducted at Peking University (2022) found that while antidepressants reduced depressive symptoms by 45% within the first two months, students who completed a full CBT course showed greater emotional resilience and lower relapse rates in the following year.

In long-term treatment, CBT has demonstrated superior efficacy in preventing relapse compared to pharmacotherapy alone. Studies suggest that about 40-60% of individuals who discontinue antidepressants relapse within one year, whereas those who undergo CBT show a 30-50% lower relapse risk due to sustained cognitive and behavioral improvements. A study from Shanghai Mental Health Center (2021) indicated that students who continued antidepressants beyond 12 months had a 55% chance of relapse upon discontinuation, whereas CBT-trained students had only a 25% chance of experiencing symptom recurrence.

Another key factor in long-term treatment is psychological dependency on medication. Many students rely on antidepressants as a quick solution and may struggle with discontinuation due to withdrawal symptoms, rebound depression, or fear of symptom recurrence. In contrast, CBT fosters self-efficacy and autonomy, empowering students to manage depressive episodes independently, making it a preferred long-term strategy for many.

That said, combining CBT with pharmacotherapy has been found to be the most effective approach for students with moderate-to-severe depression, offering both immediate symptom relief and long-term coping skills. The National Health Commission of China (2022) recommends an integrated treatment approach, particularly for students facing academic stress, social anxiety, and recurrent depressive episodes.

5.2 Patient Adherence and Treatment Preferences

Patient adherence plays a crucial role in determining the success of both CBT and pharmacotherapy, yet adherence rates vary significantly due to treatment perception, side effects, and personal beliefs about mental health.

For pharmacotherapy, one of the primary reasons for low adherence is the side effects associated with antidepressants. Weight gain, sexual dysfunction, fatigue, emotional blunting, and gastrointestinal issues are among the most commonly reported concerns. A 2021 study from Fudan University found that 40% of university students prescribed antidepressants discontinued use within the first three months, citing side effects and dissatisfaction with treatment effectiveness. Additionally, male students were more likely to stop medication due to concerns about sexual dysfunction and reduced energy levels, while female students reported higher rates of discontinuation due to weight gain and emotional blunting.

Another factor affecting pharmacotherapy adherence is stigma and cultural attitudes toward medication. Many students in China hold the misconception that taking antidepressants indicates a lack of self-control or personal weakness. The societal emphasis on academic achievement and resilience makes some students hesitant to continue medication, fearing that it may be seen as a sign of psychological instability. A survey conducted at Tsinghua University (2022) found that students who perceived higher mental health stigma were 35% less likely to adhere to their prescribed antidepressants compared to those

with a more accepting view of psychiatric medication.

CBT adherence, on the other hand, is influenced by factors such as time commitment, emotional openness, and engagement with therapy homework. While CBT is a highly effective intervention, it requires active participation, self-reflection, and consistency, which can be challenging for students with high academic workloads, avoidance tendencies, or difficulties expressing emotions. Male students, in particular, show lower adherence to CBT, as therapy often requires discussing emotions and vulnerabilities, which contradicts traditional masculine norms of self-reliance and emotional suppression.

Despite these challenges, CBT is generally preferred by students who wish to avoid medication dependence or long-term pharmacological treatment. A 2022 study from the Chinese Academy of Sciences found that 65% of university students preferred therapy-based interventions over medication, citing concerns about side effects, long-term health impact, and the desire for self-improvement. Additionally, students who completed at least 10 CBT sessions reported greater long-term satisfaction with their treatment outcome compared to those who relied solely on medication.

Gender also plays a role in treatment preference and adherence. Female students tend to favor CBT, as it allows for emotional expression, interpersonal exploration, and self-reflective growth, aligning with their coping styles and communication patterns. Male students, however, show higher initial adherence to pharmacotherapy, as medication requires less active participation and offers quicker relief without the emotional introspection that therapy demands. However, male students also have higher dropout rates from pharmacotherapy, often due to side effects, skepticism about medication effectiveness, or reluctance to seek long-term psychiatric care.

To enhance adherence rates for both treatments, several strategies can be implemented:

- For pharmacotherapy: Medical professionals should offer personalized medication plans with minimal side effects, provide clear education on expected outcomes, and integrate psychiatric follow-ups to monitor patient well-being.
- For CBT: Universities should promote therapy awareness, offer flexible scheduling, and incorporate alternative CBT models such as brief therapy sessions, digital CBT platforms, or structured behavioral interventions to accommodate different student needs.
- For combination treatment: Mental health professionals should emphasize the benefits of integrative treatment, helping students understand that medication and therapy serve complementary roles rather than opposing methods.

6. Challenges in Implementing Mental Health Interventions in Chinese Universities

Despite growing awareness of mental health issues among university students in China, the implementation of effective psychological interventions—such as Cognitive Behavioral Therapy (CBT) and pharmacotherapy—faces multiple challenges. These barriers stem from societal stigma, resource limitations, institutional constraints, and cultural attitudes toward mental health care. Addressing these challenges is critical for ensuring that students receive timely and effective treatment, reducing the long-term consequences of untreated depression.

One of the most significant barriers is mental health stigma, which remains deeply rooted in Chinese society. Many students and their families perceive mental health issues as a sign of personal weakness or failure, leading to reluctance in seeking professional help. A 2021 survey conducted by Peking University found that over 60% of Chinese university students with depressive symptoms hesitated to seek treatment due to fear of being labeled as mentally unstable. This stigma is particularly strong among male students, who may feel pressured to conform to traditional ideals of masculinity, discouraging emotional expression and psychological support-seeking.

Limited availability of trained mental health professionals in universities is another major challenge. While China has made significant strides in expanding mental health services, the ratio of licensed psychologists to university students remains low. According to data from the Chinese Ministry of Education (2022), the average ratio of mental health counselors to

students in Chinese universities is approximately 1:4,000, far below the recommended standards set by the World Health Organization. This shortage results in long waiting times for counseling sessions, making it difficult for students in crisis to receive immediate intervention. Additionally, many university counselors are overburdened with administrative duties, limiting the quality and depth of psychological support they can provide.

The integration of mental health interventions into university policies and academic systems also presents challenges. Many universities prioritize academic performance over student well-being, creating an environment where mental health concerns are often overlooked. Unlike Western educational institutions, which frequently incorporate mental health awareness into student orientation and curriculum, Chinese universities rarely have structured mental health education programs. A 2022 study from Fudan University found that only 35% of Chinese universities offer mandatory mental health courses, and even when available, these courses are often viewed as secondary to academic subjects. Without institutional prioritization, students struggling with depression may lack the necessary support to manage their condition effectively.

Another challenge lies in the over-reliance on pharmacotherapy and the underutilization of psychotherapy. While antidepressants are widely available and relatively accessible, many university health centers lack structured CBT programs or qualified psychotherapists. This leads to an imbalance in treatment options, where students experiencing depression may only receive medication without psychological support, despite evidence suggesting that CBT combined with pharmacotherapy yields the best long-term outcomes. The cost of therapy is also a barrier, as private psychological counseling remains expensive, often making CBT inaccessible for students from lower-income backgrounds.

Furthermore, cultural attitudes toward therapy and counseling differ from Western perspectives, affecting the willingness of students to engage in psychotherapy. In China, seeking external help for emotional distress is often seen as unnecessary, as students are expected to rely on family, close friends, or self-discipline to manage psychological difficulties. Many students do not fully understand the benefits of structured therapy and may prefer alternative coping mechanisms, such as academic distraction, exercise, or social withdrawal. A 2022 survey from the Shanghai Mental Health Center found that 50% of university students diagnosed with depression chose to manage their symptoms without professional intervention, fearing that therapy sessions might expose them to social judgment or academic disadvantages.

University faculty and administrators often lack mental health training, which contributes to low awareness and inadequate support for struggling students. Professors and academic advisors may not recognize the signs of depression, and in many cases, students exhibiting symptoms may be mistaken for lacking motivation or academic discipline. Without proper mental health literacy among faculty, students who need help may go unnoticed or may not receive the encouragement needed to seek professional treatment.

Digital mental health interventions have been proposed as a solution to these challenges, yet they also come with limitations. Mobile apps and online therapy platforms provide convenient, anonymous, and low-cost access to psychological resources, but they cannot fully replace in-person counseling for students with moderate to severe depression. Additionally, digital interventions may not be as effective in engaging male students, who tend to prefer action-oriented solutions rather than reflective, discussion-based therapies. While AI-powered mental health chatbots and self-help platforms have shown promise, concerns regarding data privacy, effectiveness, and lack of human connection remain obstacles to widespread adoption.

To improve the effectiveness of mental health interventions in Chinese universities, a multifaceted approach is necessary. Universities must invest in expanding mental health services, increasing the number of trained professionals, and integrating psychological well-being programs into academic curricula. Additionally, nationwide efforts should focus on reducing stigma through awareness campaigns, providing affordable and culturally appropriate therapy options, and promoting blended treatment models that combine pharmacotherapy with psychotherapy. Institutions should also train faculty members in

basic mental health first aid, enabling them to recognize at-risk students and direct them toward appropriate resources.

Addressing these challenges will require policy changes, funding support, and a shift in cultural attitudes toward mental health care. By creating a supportive and accessible mental health infrastructure, Chinese universities can improve early intervention, treatment adherence, and long-term student well-being, ultimately enhancing both academic performance and personal development.

7. Implications for Personalized Treatment Approaches

The differences in how male and female Chinese university students respond to Cognitive Behavioral Therapy (CBT) and pharmacotherapy for depression highlight the need for personalized treatment approaches. Given the complexity of depression and the varying biological, psychological, and social factors influencing treatment effectiveness, a one-size-fits-all model is insufficient. Instead, tailoring treatment plans to individual symptom profiles, gender-related differences, and personal preferences can improve adherence, efficacy, and long-term mental health outcomes.

One of the key advantages of personalized treatment is the ability to match therapeutic interventions with the unique needs of each student. Research suggests that male students tend to prefer structured, goal-oriented treatments, such as brief CBT interventions focused on behavioral activation and problem-solving strategies. In contrast, female students often benefit from therapy that incorporates emotional expression, interpersonal skills training, and deeper cognitive restructuring. A 2022 study from Peking University found that males responded better to action-based therapies, with 45% showing improvement in symptoms after engaging in structured CBT modules, while females had a 50% improvement rate in therapies emphasizing emotional regulation and interpersonal connection.

Personalization also extends to treatment modality and format. Digital mental health interventions, such as AI-driven CBT apps, online counseling, and guided self-help modules, have gained popularity among university students. However, gender differences in engagement with digital therapy must be considered. Male students may be more inclined to use self-guided, gamified mental health apps, whereas female students may prefer interactive support from therapists. A 2021 survey at Fudan University found that 60% of male students were more comfortable using anonymous online CBT programs, compared to only 38% of female students, who preferred a hybrid approach combining in-person therapy with digital support tools.

In pharmacotherapy, dosage, medication type, and side effect profiles must also be tailored to individual patients. Females are more susceptible to medication-induced weight gain, hormonal fluctuations, and emotional blunting, whereas males often experience sexual dysfunction, fatigue, or emotional numbing when using antidepressants. By incorporating biomarker testing, genetic screening, and patient-reported side effect monitoring, psychiatrists can optimize medication regimens to reduce adverse effects and improve compliance. Studies from the Shanghai Mental Health Center (2022) indicate that students who received personalized medication adjustments based on side effect management had a 30% higher adherence rate compared to those on standard prescriptions.

Cultural factors also play a role in personalized treatment selection. Traditional Chinese attitudes toward mental health often emphasize self-reliance, academic perseverance, and familial duty, leading some students to reject therapy or medication due to fear of stigma. A personalized approach should incorporate psychoeducation, helping students understand that seeking mental health support does not indicate weakness but rather a proactive step toward well-being. Furthermore, integrating traditional Chinese medicine (TCM) approaches, such as mindfulness practices, acupuncture, or herbal supplements, into treatment plans may improve acceptance and adherence among students with strong cultural affiliations.

Personalized treatment approaches must also consider the severity of depression. Mild to moderate depression may be effectively managed through CBT alone, while moderate to severe cases may require a combination of pharmacotherapy and psychotherapy. Blended models of care, where students receive medication for immediate symptom relief while concurrently building long-term coping strategies through CBT, have shown superior

outcomes in preventing relapse. According to a 2021 report from the Chinese Psychological Society, students undergoing combined treatment had a 55% lower relapse rate than those relying solely on either medication or therapy.

Another critical aspect of personalized mental health care is flexibility in treatment delivery. University students often experience high academic pressure and time constraints, making traditional weekly therapy sessions difficult to maintain. Institutions should offer flexible treatment formats, such as drop-in counseling, short-term intensive CBT programs, and asynchronous text-based therapy options, allowing students to engage with mental health support in ways that fit their schedules. A 2022 study from Tsinghua University found that students with access to flexible therapy formats had a 40% higher likelihood of completing treatment compared to those in rigid weekly programs.

To implement effective personalized treatment strategies, Chinese universities must expand mental health screening services, train counselors in gender-responsive therapy approaches, and develop integrated care models that combine clinical, digital, and holistic interventions. By shifting toward a student-centered approach, universities can increase mental health accessibility, reduce treatment dropout rates, and enhance overall well-being among Chinese university students.

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Research Progress of Radiomics and Deep Learning in Prognosis and Efficacy Prediction of Laryngeal Cancer

Huan Jiang[1] & Juan Peng[1]

[1] Department of Radiology, The First Affiliated Hospital of Chongqing Medical University, Chongqing 400016, China
Correspondence: Juan Peng, Department of Radiology, The First Affiliated Hospital of Chongqing Medical University, Chongqing 400016, China.

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Abstract

In recent years, the rapid development of radiomics and deep learning (DL) technologies has provided new research directions for the precision diagnosis and treatment of laryngeal cancer. This article introduces the concepts of radiomics and DL, and reviews the applications in predicting the prognosis and treatment efficacy of laryngeal cancer. The article highlights the limitations and challenges of radiomics and DL in laryngeal cancer, and suggests future directions such as multi-center collaboration, the establishment of standardized processes, and the integration of multi-omics approaches.

Keywords: radiomics, deep learning, laryngeal cancer, prognosis prediction, efficacy prediction

1. Introduction

Laryngeal cancer, a highly invasive malignancy of the head and neck, accounts for over 268,000 new cases globally each year, resulting in approximately 138,000 deaths (Siegel R L, Miller K D, Fuchs H E, et al., 2022). Despite significant advances in treatment techniques, the recurrence rate remains as high as 30%, and the 5-year overall survival rate is approximately 54-61% (Keek S A, Wesseling F W R, Woodruff H C, et al., 2021). Currently, the prognosis of laryngeal cancer primarily relies on the tumor-node-metastasis (TNM) staging system. However, the TNM system is mainly based on anatomical information and cannot fully reflect the biological heterogeneity of tumors, nor does it adequately evaluate the tumor microenvironment and molecular characteristics. As a result, patients with the same stage may have significantly different prognostic outcomes, thus limiting its application in personalized treatment (Liu Y, He S, Wang X L, et al., 2021). Common clinical methods for assessing laryngeal cancer prognosis and efficacy include laryngoscopy, CT, and MRI; however, the analysis of these images heavily depends on the physician's experience and subjective judgment, making it a time-consuming and labor-intensive process with uncertain accuracy.

In recent years, imaging-based artificial intelligence research has become a hotspot in the medical field (Bera K, Braman N, Gupta A, et al., 2022). Radiomics and deep learning (DL),

important branches of machine learning, enable the identification of features not visible to the human eye and quantify the temporal and spatial heterogeneity of tumor tissues. These technologies have shown great potential in tumor prognosis prediction and efficacy evaluation (Sahoo P K, Mishra S, Panigrahi R, et al., 2022; Qi M, Zhou W, Yuan Y, et al., 2024; Gu J, Wang A, Lin Q, et al., 2021). The basic workflow of radiomics includes image acquisition and preprocessing, region of interest segmentation, feature extraction and selection, and model construction and validation (Peng Z, Wang Y, Wang Y, et al., 2021). Radiomic features include first-order statistical features (e.g., mean, variance), spatial geometric features (e.g., shape, size), texture features (e.g., gray-level co-occurrence matrix), and frequency domain features (e.g., wavelet features). DL, inspired by the structure of the brain's neural network, generates various models using deep neural networks to analyze data and output predictions (Akay A & Hess H., 2019). Convolutional neural networks (CNNs), one of the most commonly used DL models in medical image analysis, automatically detect and segment lesions from images, extract and learn representative features, and construct end-to-end predictive models with layers including the input layer, hidden layers, and output layer (Avanzo M, Wei L, Stancanello J, et al., 2020). Compared to radiomics, DL models do not require predefined features and can automatically analyze complex information in medical images, significantly improving the efficiency and accuracy of image analysis. Additionally, deep learning-based radiomics (DLR) models have emerged, further exploring and identifying complex tumor characteristics, offering broader application prospects (Gu B, Meng M, Xu M, et al., 2023; Wei Z, Xv Y, Liu H, et al., 2024). This paper systematically reviews the research progress of radiomics and DL technologies in predicting the prognosis and treatment efficacy of laryngeal cancer, analyzes the challenges, and prospects future development directions to provide theoretical support for precision medicine in this field.

2. Applications of Radiomics and DL in Prognostic and Efficacy Prediction of Laryngeal Cancer

2.1 Survival Prediction

Accurate survival prediction is critical in clinical decision-making and treatment planning. CT imaging is one of the key methods in the imaging follow-up of laryngeal cancer patients, and the value of CT-based radiomics in predicting survival has been demonstrated in multiple studies (Rajgor A D, Kui C, Mcqueen A, et al., 2024; Agarwal J P, Sinha S, Goda J S, et al., 2020). Chen et al. extracted and selected texture features from enhanced CT images of 136 surgically treated laryngeal cancer patients, constructed a radiomics nomogram, and combined it with clinical and pathological factors to assess overall survival (OS). The results showed that the nomogram's C-index was significantly higher than that of the TNM staging system (0.913 vs. 0.699), and Cox proportional hazards regression analysis suggested that radiomics features were potential prognostic biomarkers for laryngeal cancer (Chen L, Wang H, Zeng H, et al., 2020). Li et al. focused on dual-energy CT images of 118 early-stage glottic laryngeal cancer patients, extracting radiomics features and using Cox and LASSO regression analysis to select the five best features for radiomics scoring, which predicted progression-free survival (PFS). The radiomics model demonstrated the best performance in the validation set, with AUCs of 0.714 and 0.671 for 1-year and 3-year PFS, respectively, surpassing those of the T-stage clinical model (AUCs of 0.607 and 0.665) (Li W, Zhang H, Ren L, et al., 2022). Notably, not only tumor-related radiomics features but also those from the surrounding environment contain valuable prognostic information. Lin et al. enrolled 92 laryngeal and hypopharyngeal cancer patients receiving radiation therapy, extracting radiomics features from pre-treatment and on-treatment CT images of both the tumor and peritumoral region (5mm beyond the primary tumor). They constructed models using LASSO-Cox regression to predict OS. The results demonstrated that the radiomics models for both the peritumoral and intratumoral regions during radiation therapy offered the best prediction performance, with AUC values of 0.77 and 0.79, respectively, both exceeding the TNM staging (AUC = 0.52) (Lin C H, Yan J L, Yap W K, et al., 2023). MRI, alongside CT, plays a crucial role in laryngeal cancer prognosis. Yuan et al. extracted radiomics features from T2-weighted MRI images of 170 head and neck squamous cell carcinoma (HNSCC) patients. By combining these features with clinical data, they developed a nomogram to predict OS and risk stratification in laryngeal

cancer patients. The fusion model exhibited a higher C-index than the TNM staging system (0.72 vs 0.61) (Yuan Y, Ren J, Shi Y, et al., 2019). Functional MRI, such as diffusion-weighted imaging (DWI), transcends the limitations of traditional MRI by providing additional information about tissue cellular function. DWI reflects the diffusion of free water at the molecular level and quantifies it using the apparent diffusion coefficient (ADC), which has shown preliminary applications in predicting the prognosis of laryngeal cancer. Tomita et al. utilized a DL model based on DWI and ADC to predict PFS in 70 laryngeal and hypopharyngeal cancer patients undergoing radiation therapy. The study revealed that the DWI-based DL model during treatment was significantly associated with PFS, and multivariable Cox analysis confirmed it as an independent prognostic factor (Tomita H, Kobayashi T, Takaya E, et al., 2022). These studies highlight the significant role of radiomics and DL in predicting the survival of laryngeal cancer patients, offering more accurate prognostic assessments compared to traditional TNM staging systems. When combined with clinical independent risk factors, they enhance predictive performance, thereby furnishing more effective tools for clinical diagnosis and treatment.

2.2 Lymph Node Metastasis Prediction

Lymph node metastasis (LNM) status serves as a critical determinant not only for optimizing treatment strategies in laryngeal cancer patients but also as a pivotal prognostic indicator affecting survival and postoperative recurrence (Le H, Chen S, Li Y, et al., 2019). Conventional imaging-based LNM diagnosis primarily depends on morphological features such as short diameter, shape, necrosis, and enhancement patterns (Valizadeh P, Jannatdoust P, Pahlevan-Fallahy M T, et al., 2024). However, these methods' accuracy often fluctuates due to inter-observer variability and subjective interpretation limitations. Radiomics and DL methodologies offer transformative potential through non-invasive, objective, and quantitative extraction of multi-dimensional imaging data, significantly enhancing predictive capabilities. Zhao et al. developed a nomogram by integrating radiomics features from venous-phase CT images of 464 laryngeal cancer patients with tumor location and lymph node status from CT reports, achieving superior predictive performance compared to radiologists' manual assessments (AUC = 0.89 vs. 0.70). Decision curve analysis further validated its clinical utility in cervical LNM prediction (Zhao X, Li W, Zhang J, et al., 2023). Jia et al. advanced this approach by manually segmenting primary tumors from enhanced T1WI and T2WI MRI sequences in 117 laryngeal cancer patients to generate radiomics signatures. When combined with MR-reported lymph node status, their nomogram demonstrated enhanced predictive accuracy over manual interpretation in both training (AUC = 0.930 vs. 0.824) and testing cohorts (AUC = 0.883 vs. 0.772) (Jia C, Cao Y, Song Q, et al., 2020). Not only can radiomics features derived from the primary tumor predict cervical LNM, but features can also be directly extracted from the lymph nodes for modeling. Wang et al. constructed a predictive model using radiomics features extracted from preoperative enhanced T1WI and DWI images of cervical lymph nodes in 120 HNSCC patients, alongside ADC values and short-axis diameters. This model achieved robust predictive performance (AUC = 0.83), surpassing ADC-alone (AUC = 0.560) and short-axis diameter-based models (AUC = 0.731) (Wang Y, Yu T, Yang Z, et al., 2022).

In addition, for laryngeal cancer patients with clinically undetected cervical LNM on preoperative imaging, there remains a risk of occult cervical LNM. Clinically, these patients are often treated with prophylactic selective neck dissection. However, compared to a conservative observation strategy, this method has not significantly improved survival rates and may lead to complications that impact quality of life (Patel T R, Eggerstedt M, Toor J, et al., 2021). Therefore, accurately predicting occult LNM preoperatively is crucial for laryngeal cancer prognosis. Wang et al. enrolled 553 clinically N0-staged laryngeal cancer patients and constructed various models, including 2D and 3D DL models, as well as a DLR model, based on primary tumor venous phase CT images to predict occult LNM. The results showed that the decision fusion-based DLR model achieved the highest AUC (0.89-0.90) across all test sets (Wang W, Liang H, Zhang Z, et al., 2024). These studies highlight the promising role of radiomics and DL in predicting cervical LNM in laryngeal cancer, not only improving accuracy but also providing more objective evidence for clinical

decision-making, thus avoiding unnecessary surgeries.

2.3 Tumor Recurrence Prediction

Despite advances in treatment, the recurrence rate of laryngeal cancer remains high, especially within the first three years after curative treatment, with approximately 30% of patients facing recurrence, which poses a major obstacle to long-term survival (Pfister D G, Spencer S, Adelstein D, et al., 2020). Therefore, accurately identifying laryngeal cancer patients at risk of recurrence and implementing early intervention is crucial. Yao et al. constructed a radiomics model using enhanced CT images from 140 laryngeal cancer patients before surgery and combined it with relevant clinical factors to develop a nomogram to predict early postoperative recurrence risk. The results showed that the nomogram's AUC was significantly higher than the clinical model (0.939 vs. 0.817) (Yao Y, Jia C, Zhang H, et al., 2023). Cong et al. extracted radiomics features from PET/CT images of 298 HNSCC patients (including 45 laryngeal cancer patients) before treatment and built a fusion model combining age, tumor location, and N-stage to predict local recurrence. The fusion model performed the best with an AUC and C-index of 0.70 (Cong H, Peng W, Tian Z, et al., 2021). Tomita et al. employed an Xception-based DL model to analyze DWI and ADC images from 70 laryngeal and hypopharyngeal cancer patients before and during treatment to predict local recurrence. The DWI-based DL model outperformed clinical staging models in predicting local recurrence, yielding an AUC of 0.767 and 81.0% accuracy in the validation cohort, compared to clinical models with AUC = 0.544 and 47.6% accuracy (Tomita H, Kobayashi T, Takaya E, et al., 2022). Collectively, radiomics and DL models exhibit substantial advantages over clinical models in post-treatment recurrence prediction. However, further validation in larger, external cohorts is warranted to enhance generalizability.

2.4 Prediction of Prognostic Tumor Molecular Markers

In recent years, radiomics and DL have attracted considerable attention in predicting prognostic tumor molecular markers in laryngeal cancer. Traditional detection methods often rely on invasive tissue samples for analysis, but artificial intelligence provides a non-invasive solution for predicting tumor molecular markers. Several studies have demonstrated that radiomics and DL can effectively predict molecular markers related to laryngeal cancer prognosis, such as Ki-67, TP53, and EGFR. Zheng et al. collected enhanced CT and Ki-67 immunohistochemical data from 217 HNSCC patients (including 66 laryngeal cancer patients) and extracted radiomics features to construct a nomogram to predict Ki-67 expression in HNSCC. The results showed that the nomogram's performance was superior to clinical models (AUC = 0.832 vs. 0.685), highlighting the added value of radiomics in model enhancement (Zheng Y M, Chen J, Zhang M, et al., 2023). Tian et al. established a radiomics model using multi-phase CT images from 96 laryngeal cancer patients to predict TP53 status. Using ANOVA and LASSO regression analysis, they identified 22 features related to TP53 status and built models using five machine learning methods, with the linear SVM radiomics model showing the best performance (AUC = 0.797) (Tian R, Li Y, Jia C, et al., 2022). Another study by Zheng et al. constructed a DLR nomogram from venous phase CT images of 300 HNSCC patients (including 97 laryngeal cancer patients) to predict EGFR mutation status. The nomogram integrated five radiomics features, six DL features, and two clinical factors (gender and necrosis area) and performed optimally in the testing set with an AUC of 0.875, demonstrating the advantages of combining radiomics and DL features (Zheng Y M, Pang J, Liu Z J, et al., 2024).

Although DL applications in predicting molecular markers for laryngeal cancer are not yet widespread, its potential and advantages have already been shown in other tumors of the head and neck, such as thyroid cancer, glioblastoma, and meningioma (Wang C W, Muzakky H, Lee Y C, et al., 2023; El Nahhas O S M, Loeffler C M L, Carrero Z I, et al., 2024; Chen J, Xue Y, Ren L, et al., 2024). In the future, as radiomics and DL technologies continue to develop and optimize, and as the quality and quantity of imaging data improve, their application in predicting molecular markers in laryngeal cancer will likely have broader prospects.

2.5 Prediction of Efficacy Prediction

Radiation therapy and chemotherapy are key treatments for laryngeal cancer patients, but the efficacy varies across individuals. Identifying robust biomarkers to predict treatment sensitivity is therefore crucial for enabling

personalized therapeutic strategies and optimizing clinical outcomes. Current clinical evaluations primarily depend on post-treatment imaging or histopathological assessments categorized as complete response, partial response, stable disease, or progressive disease. However, these conventional methods inherently suffer from temporal delays due to their reliance on post-intervention data acquisition. By contrast, radiomics and DL methodologies enable non-invasive pre-treatment prediction of therapeutic response, offering actionable insights for treatment customization. The NCCN guidelines advocate induction chemotherapy prior to total laryngectomy for advanced-stage patients to improve laryngeal preservation rates (Pfister D G, Spencer S, Adelstein D, et al., 2020). However, this approach risks cumulative toxicities, underscoring the need for precise identification of non-responders. Kang et al. constructed a radiomics model using contrast-enhanced CT images to predict pathological response (complete or partial response) in 114 advanced laryngeal cancer patients undergoing induction chemotherapy. The model achieved AUCs of 0.87 and 0.79 in the training and validation sets, respectively, and multivariate logistic regression analysis identified that only radiomics scores were significantly associated with pathological response. Furthermore, they combined radiomics scores, tumor volume, and N-stage to construct a nomogram for predicting 1-year OS, with a C-index of 0.735 in the validation set, higher than T-stage (C-index = 0.543) and N-stage (C-index = 0.561) (Kang C, Sun P, Yang R, et al., 2023). In the immunotherapy realm, PD-1 expression critically guides treatment decisions. Zandberg et al. extracted radiomics features from pre-treatment CT images of 61 HNSCC patients (including 12 laryngeal cancer patients) receiving anti-PD-1 treatment and used the XGBoost machine learning algorithm to construct a radiomics model for predicting disease control rate (complete response, partial response, or stable disease). The radiomics model outperformed clinical models based on neutrophil-to-lymphocyte ratio and HPV status, with AUCs of 71.21%, 50.03%, and 46.97%, respectively (Zandberg D P, Zenkin S, Ak M, et al., 2025). For locally advanced HNSCC patients, combining PD-1 inhibitors with chemotherapy can improve the response rate of neoadjuvant therapy (Vos J L, Elbers J B W, Krijgsman O, et al., 2021). Lin et al. included 172 HNSCC patients from three hospitals who underwent surgery after receiving neoadjuvant chemoradiotherapy, extracting radiomics features from both the tumor and surrounding regions in MRI images. They constructed corresponding radiomics scores for these regions and combined them with clinical pathological features to develop a nomogram for predicting pathological complete response. The nomogram demonstrated the highest predictive accuracy, with AUCs of 0.860 and 0.849 in the internal and external validation groups (Lin P, Xie W, Li Y, et al., 2024). In guiding post-operative adjuvant chemoradiotherapy for laryngeal cancer patients, Howard et al. constructed three machine learning models, including DeepSurv, to predict treatment benefit in 33,527 HNSCC patients, of whom 5,631 had laryngeal cancer. The results demonstrated that patients who followed the machine learning model recommendations for post-operative radiotherapy had significant survival advantages, with a risk ratio of 0.79-0.90 and C-indexes of 0.691-0.695 (Howard F M, Kochanny S, Koshy M, et al., 2020). These studies suggest that radiomics and DL offer new perspectives and methods for predicting treatment response in laryngeal cancer patients, enabling earlier non-invasive efficacy evaluation and exhibiting higher accuracy compared to clinical models.

3. Limitations and Future Outlook

Despite the significant potential of radiomics and DL methodologies in predicting laryngeal cancer prognosis and treatment efficacy, several challenges persist: (1) Most studies rely on single-center cohorts with limited sample sizes and retrospective designs, which inherently compromise the generalizability and robustness of their conclusions. Future investigations should prioritize multicenter collaborations, expanded prospective cohorts, and standardized study protocols to enhance model transferability. (2) The lack of standardized image acquisition parameters, the complexity and subjectivity of manual segmentation, as well as differences in parameter settings and algorithm selection, all contribute to poor accuracy and reproducibility of the research results. Therefore, it is essential to establish unified and standardized imaging data collection methods and precise automatic image segmentation techniques to ensure the reliability of the models. (3) The “black-box”

issue of DL limits the interpretability of the results and hinders its clinical application. Thus, increasing model transparency and interpretability should be a key direction for future research. (4) Currently, most radiomics research is focused on single-modal and single-omics studies, with relatively few studies combining multiple modalities or multi-omics. Pathology, metabolomics, and proteomics also contain valuable micro-information related to prognosis. Future studies should integrate multi-omics to uncover the systemic regulatory relationships in tumorigenesis and development from a molecular mechanism perspective, offering new insights and methods for precision treatment and prognosis prediction in laryngeal cancer.

4. Conclusion

In conclusion, radiomics and DL technologies demonstrate significant potential in predicting laryngeal cancer outcomes, including survival, recurrence, metastasis, treatment responses, and molecular biomarkers. They offer preoperative, non-invasive tools to assess prognosis and treatment efficacy. Future advancements will rely on multi-center collaborations to establish standardized analytical pipelines and validation datasets, enhancing model generalizability and robustness. Integration of multi-dimensional data (clinical, imaging, pathological, genetic) will further refine predictive accuracy, enabling personalized treatment strategies. As these technologies mature, they are poised to become pivotal in laryngeal cancer management, driving precision medicine forward.

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Research Progress of Transcutaneous Acupoint Electrical Stimulation in Perioperative Applications

Weizhuang Jia[1,2], Lihui Yue[2], Jing Han[2], Tianzhong Jia[1,2], Junlong Li[2,3] & Xichun Zhu[2]

[1] North China University of Science and Technology, Tangshan, Hebei 063210, China
[2] Pain Department of Hebei Provincial People's Hospital, Shijiazhuang, Hebei 050051, China
[3] Hebei North University, Zhangjiakou, Hebei 075000, China
Correspondence: Xichun Zhu, Pain Department of Hebei Provincial People's Hospital, Shijiazhuang, Hebei 050051, China.

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Abstract

Transcutaneous Electrical Acupoint Stimulation (TEAS), as a non-invasive treatment method, has been increasingly applied in the perioperative period due to its simplicity, non-invasiveness, and high patient acceptance. It has shown certain effects in reducing postoperative complications and promoting postoperative recovery. This review summarizes the research progress of TEAS in perioperative analgesia, improvement of neurocognitive disorders, immune function regulation, alleviation of sleep disturbances, promotion of postoperative recovery, and organ protection, aiming to provide more reference for its clinical application.

Keywords: Transcutaneous Acupoint Electrical Stimulation, perioperative, pain, autonomic nervous system, stress

1. Introduction

Since the beginning of the 21st century, with the progress of medical technology and the improvement of living standards, the number of surgeries has been increasing year by year, and people's pursuit of safety and comfort during the perioperative period has gradually increased. The perioperative period refers to the entire process from preoperative preparation to postoperative recovery, including the preoperative preparation stage, the intraoperative maintenance stage, and the postoperative recovery stage. Perioperative management is a complex and necessary process that involves the cooperation of multiple disciplines and requires the joint efforts of surgeons, anesthesiologists, and nurses. By optimizing perioperative management, not only can the patient's hospital experience be improved, but the quality of postoperative recovery can also be significantly enhanced (SIBLEY D, SELLERS D, RANDALL I, et al., 2023). Improving the perioperative experience for patients, reducing the pain, tension, anxiety, and postoperative adverse reactions they experience during medical treatment, thereby providing comfortable and reliable medical services (KOLCABA K Y., 1992). People's demands during the perioperative period mainly focus on pain management, psychological support, rapid postoperative

recovery, and the medical environment and services. During surgery or examinations, patients expect effective pain management to alleviate or eliminate pain; at the same time, an increasing number of people are paying attention to psychological comfort, hoping that medical staff can help reduce anxiety and fear, and relieve psychological stress (Teng Yunpeng & Xue Rongliang, 2023). In addition, rapid postoperative recovery is also an important part of people's medical needs. Patients hope to recover quickly after surgery, shorten their hospital stay, and return to normal life as soon as possible.

Transcutaneous Electrical Acupoint Stimulation (TEAS) is an innovative treatment method developed based on Transcutaneous Electrical Nerve Stimulation (TENS). TEAS integrates traditional Chinese medicine theories with modern technology, regulating Qi and blood, balancing Yin and Yang, and promoting recovery by electrically stimulating specific acupoints, thereby enhancing patient comfort during the perioperative period. Its theoretical foundation includes core concepts of traditional Chinese medicine such as meridians, Qi and blood, Yin-Yang balance, and holistic views (Lou Xinfa & Jiang Songhe, 2012). The mechanism of action of TEAS is closely related to neural pathways. It activates acupoints through electrical stimulation, regulates the transmission of nerve signals, and thereby affects the central nervous system and peripheral nerve functions to exert analgesic, anti-inflammatory, and autonomic regulatory effects. In terms of acupoint selection, TEAS is designed based on the "meridians" and "collaterals" in traditional Chinese medicine theory. Although these theories have not yet been fully validated by modern anatomy and histology, clinical practice has proven their effectiveness in the treatment of various diseases. This article aims to review the mechanism of action of TEAS and its research progress in perioperative applications, and to explore its potential value in improving the patient medical experience.

2. Mechanism of Action of TEAS

2.1 Analgesic Effect

The analgesic mechanisms of TEAS are primarily based on two theories: the Gate Control Theory and the Endogenous Opioid Peptide Theory (DELEO J A., 2006).

The Gate Control Theory posits that TEAS exerts its analgesic effect by inhibiting the transmission of peripheral pain signals to the central nervous system. There are two types of nerve fibers in the skin and tissues: one type is the thick fibers (Aβ fibers) that convey peripheral tactile and pressure sensations, and the other type is the thin fibers (Aδ and C fibers) that transmit peripheral pain and temperature sensations. There is a mutual inhibitory phenomenon between thick and thin fibers in signal transmission. TEAS stimulates the thick fibers, thereby inhibiting the pain transmission of the thin fibers, achieving the goal of pain relief.

The Endogenous Opioid Peptide Theory suggests that TEAS can promote the release of endogenous opioid peptides (MAYOR D., 2013), and different stimulation frequencies vary in promoting the release of opioid peptides in the central nervous system and the activation of major opioid receptors (CHEN X H & HAN J S., 1992). Low-frequency electrical stimulation may activate μ and δ opioid receptors in the spinal cord more, producing more endogenous opioids such as enkephalins and endorphins, mainly exerting analgesic effects through spinal neural pathways. High-frequency electrical stimulation, on the other hand, works more through κ opioid receptors, affecting neural pathways in both the spinal cord and the brain. Studies have shown that high-frequency (100 Hz) electroacupuncture stimulation can promote the release of dynorphins in the spinal cord (XIANG X H, CHEN Y M, ZHANG J M, et al., 2014), and a previous molecular biology study proved that endogenous dynorphins have a strong antinociceptive effect in the spinal cord (CHENG H Y, PITCHER G M, LAVIOLETTE S R, et al., 2002). Additionally, Ji-Sheng Han (1992) used antagonists for these three types of opioid receptors in his research, and the results showed that the analgesic effect produced by electroacupuncture was greatly reduced after the use of antagonists, further confirming that electrical stimulation exerts analgesic effects through the production of endogenous opioids. Josimari M. DeSantana's research found (2008) that alternating low and high-frequency sparse-dense waves can produce a stronger analgesic effect, and the development of tolerance to opioids is also slower compared to single-frequency electrical stimulation.

2.2 Regulation of Autonomic Nervous System Function

Anxiety is the most common psychological

health issue among patients in the perioperative period (GANDARELA L, DE A. SAMPAIO T P, MARçAL L, et al., 2024), and it is also a major cause of many adverse effects on patients, with excessive anxiety affecting surgical outcomes and increasing the risk of readmission. Therefore, it is very necessary to reduce the stress and anxiety levels of patients in the perioperative period. Anxiety is usually caused by dysregulation of the autonomic nervous system, with overactivation of the sympathetic nervous system or inhibition of the parasympathetic nervous system manifesting as an anxious state. The mechanism by which TEAS reduces preoperative anxiety may be achieved by regulating the levels of endogenous factors such as serotonin, norepinephrine, and cortisol (WU X, CHEN T, WANG K, et al., 2023). Recently, many studies have pointed out that the amygdala is a key emotional processing structure, and the functional connection between the frontal lobe regions of the brain and the amygdala is an important process for emotion management (LIU J, FANG J, WANG Z, et al., 2016). TEAS can regulate the functional connectivity disorders between the two, and by comparing the resting state and the functional magnetic resonance imaging results after one month of using TEAS, it was found that the functional connectivity of the amygdala-frontal lobe region network increased significantly, resulting in a marked reduction in anxiety and depression scores and improvement in symptoms. Additionally, TEAS can regulate other cortical and subcortical structures that affect emotions, such as the anterior cingulate cortex, locus coeruleus, and medial prefrontal cortex (ARANBERRI RUIZ A, 2024).

Heart Rate Variability (HRV) is one of the important indicators of autonomic nervous function. M Khawar Ali et al. (2023) analyzed 73 articles on the autonomic function of functional gastrointestinal diseases such as gastroesophageal reflux disease and irritable bowel syndrome and found that in these patients, HRV usually shows reduced parasympathetic activity or increased sympathetic activity. By monitoring changes in HRV, TEAS can increase vagal excitability, reduce sympathetic excitation, and improve gastric slow-wave motility to promote the recovery of gastrointestinal function (HU Y, ZHANG B, SHI X, et al., 2020). Wei Gao et al. (2021) conducted a multicenter randomized controlled trial and found that TEAS significantly reduced the incidence of postoperative paralytic ileus. Patients who received TEAS treatment had a noticeable increase in serum acetylcholine levels within 72 hours postoperatively, indicating that TEAS may promote the recovery of gastrointestinal function after surgery by activating the vagus nerve.

2.3 Neurochemical Mechanisms

TEAS may exert its effects by influencing the secretion of hormones and neurotransmitters. Yong-Liang Chi et al. (2019) found in a study of elderly patients undergoing knee surgery that TEAS could reduce the levels of cortisol, adrenocorticotropic hormone, and C-reactive protein in the blood, alleviate perioperative stress and inflammatory responses, and accelerate postoperative recovery in elderly patients. Additionally, TEAS can improve mood by affecting the levels of neurotransmitters in the brain (WU X, CHEN T, WANG K, et al., 2023), such as promoting the release of serotonin and dopamine to combat preoperative anxiety and depression. Studies have shown that TEAS can act on the brain-gut axis (BAI Y-F, GAO C, LI W-J, et al., 2020), which connects the central nervous system with the enteric nervous system, by reducing the secretion of substance P and vasoactive intestinal polypeptide, promoting the secretion of motilin and cholecystokinin, thereby affecting the sensory, motor, and endocrine patterns of the gastrointestinal tract, as well as promoting the recovery of postoperative gastrointestinal function by affecting the gut microbiota.

2.4 Organ Protection

TEAS plays a protective role in organ function during the perioperative period. There are many factors during surgery that can cause brain damage, such as reduced cerebral blood flow due to hypotension, anemia, and vasospasm, ischemia-reperfusion injury, and direct damage to cerebral blood vessels and brain tissue from the surgery itself. The key pathological mechanisms involved are oxidative stress and inflammation (CHEN G, WANG X, JIN Z, et al., 2024). Intraoperative brain injury can affect the patient's neurologic function, such as limb weakness, speech disorders, or sensory disturbances, and can even cause permanent disability. Therefore, close cooperation between surgeons, anesthesiologists, and the nursing

team is needed to reduce its occurrence. A study in a middle cerebral artery occlusion/reperfusion (MCAO/R) rat model found that TEAS can significantly reduce neuronal apoptosis, neuroinflammation, and oxidative stress injury in the hippocampus of MCAO/R rats by activating silent information regulator factor 1 (SIRT1), thereby reducing brain damage (TAN Z, DONG F, WU L, et al., 2024). TEAS preconditioning can alleviate ischemia-reperfusion injury in rats by regulating microglial polarization and neuroinflammation through the Nrf2/HO-1 signaling pathway (LI J, HAO M, LIU M, et al., 2022). TEAS can exert pulmonary protective effects by reducing oxidative stress during one-lung ventilation. Studies have shown that TEAS can lower the levels of malondialdehyde in the serum during thoracoscopy surgery, increase the activity of superoxide dismutase, and improve oxygenation indices during one-lung ventilation (JU S, LIU M, WANG B, et al., 2023).

3. Clinical Applications of TEAS in the Perioperative Period

TEAS, which combines the traditional Chinese medicine concept of acupuncture with modern electrical stimulation technology, is mainly applied in the perioperative period in the following areas:

3.1 Postoperative Analgesia

Currently, common pain management techniques include pharmacological treatment, nerve blocks, epidural analgesia, physical therapy, and patient-controlled analgesia (PCA) (RAJ P, SINHA N, KHARWAR R K, et al., 2024). Pain medications have significant analgesic effects, but they also come with relatively more side effects, such as increased damage to liver and kidney functions, nausea, and vomiting. Nerve blocks and epidural analgesia are invasive procedures that can be highly stimulating to patients and require a high level of technical skill from the operating physician. Multimodal analgesia is currently the most recommended approach, as it targets different types and intensities of pain by selecting different analgesic techniques and anesthetic drugs with different mechanisms of action to achieve a more ideal analgesic effect (BAEZ C, PRIETO H A, TISHAD A, et al., 2024). A meta-analysis including 17 clinical randomized controlled trials involving 1,375 subjects showed (WANG D, SHI H, YANG Z, et al., 2022) that patients treated with TEAS had significantly lower pain scores 24 hours after surgery, and the amount of postoperative opioid analgesics used was also significantly reduced, while the occurrence of adverse events such as dizziness, nausea, and vomiting was also decreased. Clinical trials have proven that using TEAS 30 minutes before surgery can fully activate the body's endogenous analgesic system, producing various endogenous opioid substances, thereby reducing the need for analgesic and sedative drugs and increasing patient comfort (JIANG M, WANG B, LIU M, et al., 2024). TEAS can significantly reduce pain scores within 48 hours after thoracoscopy surgery, and the number of patients requiring rescue analgesia within 24 hours after surgery is also significantly reduced (LIU J, ZHANG K, ZHANG Y, et al., 2024). TEAS has a definite analgesic effect, relatively fewer adverse reactions, minimal stimulation, and a protective effect on the body's organs, potentially becoming an important part of multimodal analgesia.

3.2 Regulation of Autonomic Nervous System Function

Mustafa Al-Zamil et al. (2024) conducted high-frequency and low-frequency electrical stimulation directly on the right median nerve to observe its effects on anxiety disorders. The results showed that patients who received electrical stimulation had significantly reduced scores on the 7-item Generalized Anxiety Disorder scale and the Hamilton Anxiety Scale, and their symptoms were also significantly alleviated within six months. Postpartum Depression (PAYNE J L & MAGUIRE J., 2019) is a common psychological disorder in women after childbirth. Current research suggests that postpartum depression is mainly related to changes in hormone levels, sleep quality, psychological stress, and dysregulation of the autonomic nervous system. The application of TEAS with different frequencies during childbirth has a positive effect on hormone levels, pain perception, and anxiety levels (SULU R, AKBAS M & CETINER S., 2022). High-frequency TEAS can promote the release of oxytocin and endorphins, reduce the level of cortisol in the blood, inhibit sympathetic nerve stimulation of the vagus nerve, and play a positive role in the postoperative recovery of mothers. Yong-Liang Chi et al. (2019) found in their study of elderly patients undergoing knee surgery that TEAS could accelerate patient

recovery by reducing perioperative stress and inflammation levels. A meta-analysis summarizing 12 randomized controlled trials involving 1,347 patients showed (JIANG M, WANG B, LIU M, et al., 2024) that the mean arterial pressure and heart rate of patients in the TEAS group were significantly lower than those in the control group immediately after extubation and up to 10 minutes later. The extubation process was more stable, reducing the stress response triggered by extubation and decreasing the risk of postoperative agitation and delirium. Patients who received TEAS had significantly lower levels of high-sensitivity troponin T postoperatively and improved heart rate variability indicators, indicating that TEAS can reduce postoperative myocardial damage and improve autonomic function (LI H, WU C, YAN C, et al., 2019).

TEAS applied in patients with sleep disturbances during the perioperative period can significantly reduce inflammatory responses and improve postoperative sleep quality. Data shows that more than 40% of patients exhibit sleep disturbances on the first postoperative day, and sleep issues may persist for several days (CHOUCHOU F, KHOURY S, CHAUNY J-M, et al., 2014). Decreased sleep quality can lead to numerous harms, such as exacerbating patients' anxiety and irritability, inducing Postoperative Delirium (POD), reducing immunity, and delaying postoperative recovery. TEAS can stimulate specific acupoints, thereby activating the nervous regulatory system, which helps regulate the neurotransmitters in the brain related to sleep, thus improving patients' sleep quality (WEI W, HUANG X & ZHU J., 2023).

3.3 Improving Neurocognitive Function

TEAS contributes to the improvement of neurocognitive dysfunction that patients may experience during the perioperative period. Kai-Yu Huang et al. (2023), through an analysis of 12 clinical studies involving 991 patients, concluded that TEAS can reduce the incidence and duration of postoperative delirium, significantly improving the quality of patients' postoperative recovery. Fei Guo et al. (2023) conducted a meta-analysis of 12 clinical randomized controlled studies on the treatment of postoperative delirium with TEAS in recent years, showing that TEAS can protect neurons, reduce neuroinflammatory responses, and decrease the dosage of anesthetic drugs, thereby reducing the incidence of delirium within one week after surgery. Both meta-analyses demonstrated the significant effect of TEAS in improving postoperative cognitive dysfunction in patients. The randomized controlled trials involved used various scoring tools and blood indicators to assess postoperative delirium, and the comparative results all showed a significant therapeutic effect of TEAS, increasing the credibility of the findings. However, there are few more direct examinations such as imaging studies and electroencephalograms, and research in these areas should be increased to more objectively reflect the treatment effects.

3.4 Promoting Postoperative Recovery

A meta-analysis including 10 clinical studies involving 2,383 patients showed (ZHANG M, ZHANG H, LI P, et al., 2024) that TEAS can reduce the use of intraoperative opioid drugs and postoperative PCA, decrease the occurrence of postoperative nausea and vomiting, enable early recovery of gastrointestinal absorption and digestion functions, and enhance the patient's body resistance. For some orthopedic surgeries, such as total knee arthroplasty (TKA), early postoperative activity is crucial for the quality of patient recovery. The introduction of TEAS not only reduces adverse reactions from analgesic drugs but also plays a positive role in improving postoperative knee joint function (ZHANG L., 2024). The micturition reflex is mainly controlled by the autonomic nervous system; anticholinergic drugs and anesthetics can inhibit parasympathetic activity, leading to postoperative urinary retention. TEAS balances autonomic nervous function, increases the release of the micturition reflex messenger urinary ATP, and reduces the occurrence of urinary retention (HUANG K-Y, LIANG S, DU H-G, et al., 2024).

3.5 Organ Protection

TEAS contributes to the stability of liver and kidney function during the perioperative period by improving blood circulation, reducing oxidative stress, and exhibiting anti-inflammatory effects, thereby reducing the risk of ischemia-reperfusion injury (YANG X, FENG Z & CAI M., 2024). The endorphins released by TEAS not only play a role in controlling pain and reducing stress but also promote the dilation of bronchioles, alleviating dyspnea and lowering the incidence of postoperative pulmonary complications (CHEN J, ZHANG Y, LI X, et al., 2020). A meta-analysis

shows that TEAS can significantly reduce myocardial damage and protect the heart through various mechanisms, promoting the recovery of cardiac function and stabilizing circulation, with a reduction in the amount of vasoactive drugs used (ASMUSSEN S, PRZKORA R, MAYBAUER D M, et al., 2017).

3.6 Enhancing Patient Satisfaction

Patients, while focusing on the quality of treatment, also hope for the lowest possible hospitalization costs and the shortest possible hospital stays. Yilong Liu et al. through a meta-analysis of 34 clinical randomized controlled trials, demonstrated that TEAS can significantly reduce the length of hospital stay and hospitalization costs, and increase patient satisfaction (LIU Y, FAN J, ZHANG X, et al., 2024). Whether postoperative ICU stay is necessary and the duration of ICU stay are also concerns for patients. TEAS significantly improves the Quality of Recovery (QOR-15) scores on the first and second days after surgery, markedly reducing ICU stay and postoperative hospital days (JU S, LIU M, WANG B, et al., 2023). TEAS can reduce the occurrence of postoperative adverse events through the aforementioned mechanisms, decrease additional hospitalization costs and length of stay due to the management of complications, and enhance patient trust and satisfaction.

4. Summary and Prospects

The advantages of TEAS lie in its combination of the essence of traditional Chinese medicine and modern technological innovation, providing patients with a safer and more efficient treatment method. However, in current clinical research, the selection criteria for acupoint pairing in TEAS lack scientific standards, often relying on previous studies without clinical guidelines. Therefore, future research needs to focus more on large-sample, multicenter studies that concentrate on parameters and standardized selection of acupoints. This research should reveal the mechanisms of TEAS at the cellular and molecular levels, making the application of TEAS in the perioperative period more quantifiable, standardized, systematic, and objective.

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Prostate Cancer Radiotherapy: Current Status, Clinical Challenges, and Future Strategies

Xinyi Cao[1], Junming Zhu[1] & Hongbin Deng[1]

[1] Department of Oncology, Laboratory of Immunity, Inflammation & Cancer, The First Affiliated Hospital of Chongqing Medical University, Chongqing 400016, China
Correspondence: Hongbin Deng, Department of Oncology, Laboratory of Immunity, Inflammation & Cancer, The First Affiliated Hospital of Chongqing Medical University, Chongqing 400016, China.

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Abstract

The radiation therapy for prostate cancer plays a central role in the overall management of the disease, covering a wide range of applications, including radical treatment for localized tumors, postoperative adjuvant/rescue radiotherapy, and palliative treatment for advanced metastatic lesions. With the advancement of radiotherapy technologies and optimization of combined treatment strategies, the precision and safety of prostate cancer radiotherapy have significantly improved. However, key clinical challenges remain: how to determine the suitability of radical surgery or radiotherapy, balance the increase in radiation dose with toxicity control, the choice between adjuvant or salvage radiotherapy for postoperative recurrence, and the synergistic mechanisms and applicable populations for radiotherapy combined with novel endocrine drugs or immunotherapy. This article systematically reviews the current status and recent advances in prostate cancer radiotherapy, explores the management of radical radiotherapy, postoperative adjuvant radiotherapy (ART), and salvage radiotherapy (SRT), the management of radiotherapy toxicity, and individualized treatment strategies in the context of new technologies. It further investigates cutting-edge technologies such as AI-guided radiotherapy planning and Flash ultra-high-speed radiotherapy, with the aim of providing evidence-based support for clinical decision-making and research translation.

Keywords: prostate cancer, radiation therapy, toxicity management, individualized therapy, artificial intelligence, Flash ultrafast radiotherapy

1. Introduction

Prostate cancer is the second most common malignancy among men worldwide (Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al., 2021), with a continuously increasing number of new cases (James ND, Tannock I, N'Dow J, Feng F, Gillessen S, Ali SA, et al., 2024). Current treatment options for prostate cancer mainly include surgery, radiotherapy, endocrine therapy, and chemotherapy, with radiotherapy playing a particularly crucial role throughout the entire treatment process. Although the technology for prostate cancer radiotherapy is relatively mature, there are still controversies in the selection of

optimal timing of radiotherapy and the combination with endocrine therapy (Latorzeff I, Le Guevelou J & Sargos P., 2023). With advances in treatment technologies, prostate cancer radiotherapy requires greater precision and personalization to achieve a balance between minimizing clinical side effects and maximizing disease control benefits (Martin NE & D'Amico AV., 2014).

2. Radical Radiotherapy

Radical prostatectomy (RP) and radical radiotherapy (RT) are the main treatment options for intermediate- and high-risk localized prostate cancer (Hamdy FC, Donovan JL, Lane JA, Metcalfe C, Davis M, Turner EL, et al., 2023). Surgery aims to achieve cure by removing the prostate and surrounding tissues, while radiotherapy kills cancer cells through high-dose radiation. In recent years, significant advancements have been made in radiotherapy techniques, including the application of intensity-modulated radiotherapy (IMRT), stereotactic body radiotherapy (SBRT), and proton therapy, which have greatly improved the precision and efficacy of radiotherapy (Daly T., 2020). Studies have shown that no differences in overall survival or progression-free survival were observed between radical prostatectomy and radical radiotherapy, indicating that radical radiotherapy is as effective as surgery (Hamdy FC, Donovan JL, Lane JA, Metcalfe C, Davis M, Turner EL, et al., 2023). Additionally, radical radiotherapy has lower urinary toxicity, but carries a slightly higher risk of gastrointestinal issues. However, severe gastrointestinal problems and incontinence are very rare. This conclusion has been confirmed in other studies comparing radical radiotherapy with radical prostatectomy for localized prostate cancer (van As N, Yasar B, Griffin C, Patel J, Tree AC, Ostler P, et al., 2024; Chen RC, Basak R, Meyer A-M, Kuo T-M, Carpenter WR, Agans RP, et al., 2017). Clinicians should consider the short- and long-term effects of treatment on the urinary tract, gastrointestinal system, and sexual function, as well as the risks of disease progression and the patient's financial situation when choosing the most appropriate treatment.

Radical radiotherapy can also be combined with endocrine therapy (ADT) to achieve better disease control, prolonging progression-free survival and overall survival. For patients with intermediate- and high-risk localized prostate cancer, the combination of radiotherapy and ADT has been shown to significantly improve treatment outcomes, enhancing progression-free survival and overall survival rates (D'Amico AV, Manola J, Loffredo M, Renshaw AA, DellaCroce A & Kantoff PW, 2004; D'Amico AV, Chen M-H, Renshaw AA, Loffredo M & Kantoff PW., 2008; Jones CU, Hunt D, McGowan DG, Amin MB, Chetner MP, Bruner DW, et al., 2011). ADT slows prostate cancer growth by inhibiting the secretion of androgens, thereby enhancing the effectiveness of radiotherapy. However, the duration of ADT remains controversial. Some studies suggest that 4 to 6 months of ADT may be sufficient for intermediate-risk patients, while for high-risk patients, the duration of ADT may need to be longer, potentially up to 2 to 3 years (Zapatero A, Guerrero A, Maldonado X, Alvarez A, Gonzalez San Segundo C, Cabeza Rodríguez MA, et al., 2015).

3. Adjuvant Radiotherapy

Adjuvant radiotherapy (ART) is an important adjunctive treatment following radical prostatectomy for prostate cancer, aimed at reducing the risk of local recurrence and distant metastasis in high-risk patients (Daly T, Hickey BE, Lehman M, Francis DP & See AM., 2011). In recent years, several randomized controlled trials have deeply investigated the efficacy, optimal timing, and combined treatment strategies of ART, providing important evidence-based medical support for clinical practice. In studies such as SWOG 8794, patients with high-risk characteristics were included, such as pathological staging of T3N0M0 or higher, and Gleason score $\geqslant$ 7. These characteristics indicate a higher risk of recurrence following radical prostatectomy. The SWOG 8794 trial included 473 high-risk prostate cancer patients, and the results showed that patients who received ART had significantly better biochemical recurrence-free survival (bRFS), prostate cancer-specific survival (PCSS), and overall survival (OS) rates compared to the observation group. Similarly, the EORTC 22911, ARO 96-02, and FinnProstate trials consistently showed that ART has significant advantages in improving these key survival metrics (Thompson IM, Tangen CM, Paradelo J, Lucia MS, Miller G, Troyer D, et al., 2009; Bolla M, Poppel H van, Tombal B, Vekemans K, Pozzo LD, Reijke TM de, et al., 2012; Wiegel T, Bottke D, Steiner U, Siegmann A, Golz R, Störkel S, et al., 2009; Hackman G, Taari K, Tammela TL, Matikainen M, Kouri M, Joensuu T, et al., 2019).

For patients with positive lymph nodes, adjuvant radiotherapy can also offer survival benefits (Abdollah F, Karnes RJ, Suardi N, Cozzarini C, Gandaglia G, Fossati N, et al., 2014; Abdollah F, Dalela D, Sood A, Keeley J, Alanee S, Briganti A, et al., 2018; Jegadeesh N, Liu Y, Zhang C, Zhong J, Cassidy RJ, Gillespie T, et al., 2017; Touijer KA, Karnes RJ, Passoni N, Sjoberg DD, Assel M, Fossati N, et al., 2018), with even more significant survival benefits in high-risk positive lymph nodes patients (Gleason score 8-10 or three or more affected lymph nodes). Moreover, when adjuvant radiotherapy is combined with adjuvant androgen deprivation therapy, a more apparent trend of reduced mortality is observed (Froehner M, Coressel Y, Koch R, Borkowetz A, Thomas C, Wirth MP, et al., 2022). These findings suggest that postoperative adjuvant radiotherapy is an effective treatment option for high-risk prostate cancer patients.

In addition, the combination therapy strategies for ART are continually being explored. The combination of adjuvant radiotherapy with hormone therapy has been shown to significantly improve patients' disease-free survival and progression-free survival (Omrcen T, Hrepic D, Boraska Jelavic T & Vrdoljak E., 2015). Some studies indicate that long-term androgen deprivation therapy (ADT, 24 months) significantly improves progression-free survival compared to short-term ADT (6 months), although it does not improve overall survival (OS). The incidence of grade 3 or higher toxicities was 14% in the short-term ADT group and 19% in the long-term ADT group (p=0.025), but no treatment-related deaths occurred (Cc P, H K, Ad C, Nw C, Cn C, Wr C, et al., 2024). Therefore, when deciding on the duration of ADT, the benefits and adverse effects of long-term ADT need to be carefully weighed. For patients with a longer life expectancy who can tolerate the side effects of ADT, long-term ADT is recommended.

4. Salvage Radiotherapy

Salvage radiotherapy (SRT) is the standard treatment for biochemical recurrence after radical prostatectomy (Terlizzi M, Limkin EJ, Moukasse Y & Blanchard P., 2022). Studies have shown that salvage radiotherapy is one of the treatments that may cure recurrent prostate cancer, especially when treatment is started at a low prostate-specific antigen (PSA) level, which leads to better outcomes (Morgan TM, Boorjian SA, Buyyounouski MK, Chapin BF, Chen DYT, Cheng HH, et al., 2024). The NCCN guidelines recommend a radiation dose of 64-72 Gy to the prostate bed for patients with biochemical recurrence after radical prostatectomy and no distant metastasis. If there is clinically confirmed local recurrence by biopsy or imaging, the radiation dose should be increased further. For patients at risk of pelvic lymph node metastasis, a preventive dose of 45-50 Gy is recommended; for imaging-confirmed recurrent pelvic lymph nodes, the recommended dose is 60-70 Gy (Schaeffer EM, Srinivas S, Adra N, Ahmed B, An Y, Bitting R, et al., 2024). However, some trials have indicated that increasing the radiation dose to the prostate bed in patients with biochemical recurrence alone does not improve biochemical progression-free survival, but results in a higher incidence of gastrointestinal toxicity (Ghadjar P, Hayoz S, Bernhard J, Zwahlen DR, Hölscher T, Gut P, et al., 2021). The safety and efficacy of hypofractionated radiation therapy in SRT remains a question that needs to be analyzed and explored in further experiments.

The addition of endocrine therapy can provide patients with additional survival benefits. Several studies have shown that SRT combined with ADT can improve disease-free survival, progression-free survival, and overall survival (Carrie C, Magné N, Burban-Provost P, Sargos P, Latorzeff I, Lagrange J-L, et al., 2019; Dess RT, Sun Y, Jackson WC, Jairath NK, Kishan AU, Wallington DG, et al., 2020). Therefore, the combination of SRT and ADT is recommended to improve patient prognosis.

Currently, research indicates that SRT has the same disease control effect as ART but may reduce urinary and gastrointestinal toxicity (Kneebone A, Fraser-Browne C, Duchesne GM, Fisher R, Frydenberg M, Herschtal A, et al., 2020; Sargos P, Chabaud S, Latorzeff I, Magné N, Benyoucef A, Supiot S, et al., 2020; Parker CC, Petersen PM, Cook AD, Clarke NW, Catton C, Cross WR, et al., 2024). This finding has led current guidelines to recommend SRT over ART. However, the studies included in the above research have a relatively small proportion of patients with a Gleason score of $\geqslant 8$. The efficacy of SRT in this population still requires further evaluation.

5. Palliative Radiotherapy

Palliative radiotherapy for prostate cancer is a treatment method aimed at advanced or

metastatic prostate cancer, intended to alleviate symptoms, improve quality of life, and extend survival rather than cure the disease. This treatment is suitable for patients whose cancer has spread to the bones or other parts of the body or who experience pain or other discomforts. The bones are a common site for distant metastasis in prostate cancer, and after bone metastasis occurs, patients may experience pathological fractures, spinal cord compression, pain, and other bone-related events that affect their quality of life. Currently, the standard treatment for alleviating pain from metastatic lesions and preventing adverse events such as fractures caused by bone metastasis is external beam radiotherapy (Fischer-Valuck BW, Baumann BC, Apicelli A, Rao YJ, Roach M, Daly M, et al., 2018).

Prostate cancer patients with low metastatic burden (defined as ⩽4 bone metastases, with or without distant lymph node involvement) who undergo palliative radiotherapy may benefit from a 3-year overall survival rate (Müller A-C, Aebersold DM, Albrecht C, Böhmer D, Flentje M, Ganswindt U, et al., 2022). Commonly used fractionation schemes are designated as short-course treatment ([SC-RT]: 1 session of 8 Gy and 5 sessions of 20 Gy) and long-course treatment ([LC-RT]: 10 sessions of 30 Gy and 15 sessions of 37.5 Gy). Several prospective randomized trials and meta-analyses have compared the differences in pain control effects between different fractionated treatment regimens, finding similar pain control outcomes. LC-RT is associated with improved overall survival (OS), but no OS differences were observed between 37.5 Gy and a single 8 Gy session or 5 sessions of 20 Gy. Short-course treatment can reduce treatment costs and has economic advantages. LC-RT remains the most common fractionated treatment scheme for palliative bone metastasis in PCa patients, though the use of palliative SC-RT is increasing. Therefore, many medical associations, including the American Society for Radiation Oncology (ASTRO), have released practice guidelines advocating for single-session or shorter courses of radiotherapy (Fischer-Valuck BW, Baumann BC, Apicelli A, Rao YJ, Roach M, Daly M, et al., 2018).

6. Toxicity Management of Radiotherapy

Although radiotherapy can provide significant survival benefits for prostate cancer patients, its toxic side effects should not be ignored, as they can have a substantial negative impact on the patient's quality of life. Common adverse reactions to prostate cancer radiotherapy include radiation cystitis, urethral stricture, and proctitis, while less common side effects include urethral fistula, gastrointestinal fistula, and bone toxicity (Matta R, Chapple CR, Fisch M, Heidenreich A, Herschorn S, Kodama RT, et al., 2019). Currently, the toxic side effects of radiotherapy can be reduced by optimizing radiotherapy plans, using image-guided radiotherapy (IGRT) to refine the treatment process, and adopting hypofractionated radiotherapy regimens (De Bari B, Arcangeli S, Ciardo D, Mazzola R, Alongi F, Russi EG, et al., 2016).

For mild urinary or intestinal toxicity, symptomatic treatments such as pain relief and anti-inflammatory medications are typically used to alleviate symptoms. In terms of urinary system toxicity, urinary obstruction and urethral stricture are common severe adverse reactions. Acute obstruction is usually managed with catheterization and medication, while advanced obstruction may require endoscopic or surgical treatment to improve symptoms. For urethral stricture, initial treatments include dilation and/or visual endoscopic urethrotomy. After these treatments, patients may experience recurrent strictures, which may require open urethroplasty or urethral reconstruction using flaps or grafted tissue (Matta R, Chapple CR, Fisch M, Heidenreich A, Herschorn S, Kodama RT, et al., 2019).

In terms of the gastrointestinal system, rectal bleeding is a common adverse reaction. For mild toxicity, oral medications such as metronidazole combined with ciprofloxacin can be used, or local treatments such as 4% formaldehyde enemas may be applied. For refractory rectal bleeding, hyperbaric oxygen therapy may be required, as it promotes healing by stimulating capillary angiogenesis in the bladder. For grade 3 or higher proctitis, if bleeding is difficult to control, endoscopic treatment may be necessary. In some cases, surgery may be required, such as defunctioning loop colostomy, Hartmann's procedure, resection and anastomosis, or pull-through procedures. Surgery is typically considered a last resort, as these patients often have a higher risk of complications and mortality (Matta R, Chapple CR, Fisch M, Heidenreich A, Herschorn S, Kodama RT, et al., 2019).

7. Individualized Radiotherapy Strategies for Prostate Cancer

With the support of molecular biomarkers, image guidance, and artificial intelligence (AI) technologies, developing appropriate personalized radiotherapy strategies can significantly improve the precision and efficacy of radiotherapy. The Decipher score is a biomarker-based scoring tool that assesses the risk of recurrence and the likelihood of metastasis in prostate cancer patients. This tool helps identify which prostate cancer patients are more aggressive, thereby guiding treatment decisions and optimizing follow-up management (Jairath NK, Dal Pra A, Vince R, Dess RT, Jackson WC, Tosoian JJ, et al., 2021). PSMA PET/CT is a molecular imaging technology with high sensitivity and specificity, capable of accurately detecting recurrent lesions even at lower PSA levels. By accurately localizing the scope of lesions, it reduces radiation exposure to normal tissues, improving treatment efficacy. It has demonstrated significant value in salvage radiotherapy after biochemical recurrence and targeted therapy for oligometastatic lesions, greatly enhancing lesion detection capability and optimizing treatment decisions (Mena E, Lindenberg L & Choyke P., 2022). Currently, the application of artificial intelligence (AI) in prostate cancer radiotherapy management shows enormous potential. Machine learning algorithms can analyze large amounts of clinical and imaging data to optimize radiotherapy plans, ensuring maximum therapeutic effect and minimizing side effects in dose distribution (Pang Y, Wang H & Li H., 2022). Additionally, AI can be used to predict radiotherapy-related toxicities, for example, by analyzing patients' genomic data and clinical characteristics to identify high-risk patients in advance, thereby enabling preventive measures (Rydzewski NR, Helzer KT, Bootsma M, Shi Y, Bakhtiar H, Sjöström M, et al., 2023). These AI-driven models provide strong technical support for personalized radiotherapy.

8. Future Direction

Although immunotherapy has achieved significant and durable effects in certain cancer types, similar success has not been realized in prostate cancer patients. This may be related to the low mutational burden and tumor immunogenicity of prostate cancer (Alexandrov LB, Nik-Zainal S, Wedge DC, Aparicio SAJR, Behjati S, Biankin AV, et al., 2013). Radiotherapy not only directly kills tumor cells but also activates the immune system by inducing immunogenic cell death (ICD). The combination of radiotherapy and immunotherapy has shown great potential in clinical studies, but significant survival benefit has not yet been achieved in clinical trials, partly due to insufficient treatment timing or dosage strategies (Green M, Feng, Felix Y, Mehra, Rohit, & Spratt DE., 2017). Therefore, further optimization of patient selection criteria and treatment plans is needed, as well as the evaluation of novel targets and combination strategies with radiotherapy, to advance the application of immunotherapy and radiotherapy in prostate cancer.

Flash radiotherapy is an ultrahigh dose rate radiation therapy technique that can deliver a high dose of radiation in an extremely short time (usually on the millisecond scale), while minimizing damage to normal tissues and effectively killing tumor cells. Additionally, Flash radiotherapy can shorten treatment times, with the treatment time for each beam reduced from 1 minute to less than 1 second, thereby reducing instability caused by organ motion (Kaulfers T, Lattery G, Cheng C, Zhao X, Selvaraj B, Wu H, et al., 2024). Its application in prostate cancer treatment holds great potential, but further biological and clinical research is needed to validate its safety and long-term effects.

9. Discussion

Radiotherapy for prostate cancer plays a central role in the overall disease management but still faces several challenges in clinical practice. Radical radiotherapy is an important treatment option for intermediate- to high-risk localized prostate cancer, with efficacy comparable to radical surgery and lower urinary tract toxicity. However, the gastrointestinal toxicity of radical radiotherapy should not be overlooked, and careful consideration is required in clinical practice. Furthermore, the combination of radiotherapy and androgen deprivation therapy (ADT) significantly enhances treatment outcomes, but the optimal duration of ADT remains controversial. Future research should focus on further optimizing radiotherapy techniques to reduce toxic reactions and establish clear strategies for the best application of ADT. The management strategies for postoperative adjuvant radiotherapy (ART) and salvage radiotherapy (SRT) are also continuously being refined. ART has shown

significant advantages in reducing the risk of local recurrence and distant metastasis in high-risk patients, but its combination strategies, such as with endocrine therapy, still need further exploration. As the standard treatment for biochemical recurrence after radical prostatectomy, SRT is more effective at lower PSA levels, but more research is needed to determine whether adjuvant radiotherapy or salvage radiotherapy is more suitable for high-risk patients with a Gleason score of $\geqslant$8.

The management of radiotherapy toxicity is crucial for improving patients' quality of life. Although advances in radiotherapy techniques have reduced the incidence of toxic reactions, urological and gastrointestinal toxicities remain significant concerns. Optimizing radiotherapy plans, using image-guided radiotherapy (IGRT) techniques, and employing hypofractionated radiotherapy regimens can help reduce side effects to some extent. For existing toxic reactions, appropriate treatment measures should be taken based on their severity to enhance the patient's quality of life. Future directions will continue to focus on achieving better therapeutic outcomes while reducing radiotherapy-related adverse effects, which greatly requires personalized radiotherapy management and the development of new technologies. Currently, the development of cutting-edge technologies such as artificial intelligence and Flash ultrahigh-dose rate radiotherapy holds great potential for application, but their long-term effects and safety still need further verification.

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