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Review Article

Rarest cancer for Review

Rarest Cancer - A Review

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Abstract: Less than six cases per 100,000 people per year, or around 22% of all cancers diagnosed worldwide, are rare malignancies. They disproportionately impact specific demographic groups. Although it is a difficult field of research, the transmission of uncommon malignancies is not extensively covered. Studying the epidemiology of rare cancers poses significant challenges and needs to be tackled more. Despite efforts, mostly in a few European countries, there have been some slight advancements in treating uncommon tumors. The causes of this obvious stagnation are multifaceted. Still, they primarily stem from logistical challenges associated with conducting clinical trials in patient populations with very low numbers, pharmaceutical companies' reluctance to invest in niche markets, and the difficulty of gathering sufficient data to develop cost-effective medications. For example, due to the lack of profitability, pharmaceutical companies may not remain willing to invest in clinical trials in patient populations with small numbers due to the financial expenses related to performing the studies could not be worth the possible rewards. Additionally, it could be challenging to acquire the data needed for the creation of affordable treatments since it might not be accessible or might be too expensive. However, it's crucial to remember that better treatments can provide significant value to patients even if those treatments have limited profitability. A key platform for establishing new international clinical trials in rare cancers is the International Rare Cancers Initiative. This review outlines the present difficulties and problems with the analysis, treatment, and study of uncommon malignancies. However, in addition to genetic changes, it is vital to look at the roles that mutation and the cell environment play in these malignancies' development, biology, and behavior. Patients with uncommon tumors struggle because clinical trials are difficult to run in this situation due to poor accrual. Individuals with not common carcinomas will only increase as more molecular subtypes of common tumours are identified. Clinical trials and research into these cancer forms must thus adjust their focus because, according to epidemiological criteria, they will eventually become uncommon tumours. This review focuses on treatments, rare cancer initiatives, problems with the treatment, tumour detection, and experimental studies.

Keywords: Diagnoses problems - managerial challenges - rare hematologicaltumours - Worldwide Few tumours Project - uncommon malignancies - uncommon tumours in children

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1. INTRODUCTION

Those malignancies affecting a tiny portion of humanity across every demographic qualify as uncommon malignancies.[1]These malignancies affect less than 1% of the population, and while they may be more common in certain populations, they are still considered uncommon when looking at the overall population. However, those affected by these rare malignancies often face greater challenges owing to absence of awareness and resources available. An uncommon ailment, sometimes known as an infant illness, affects no more than 200,000 individuals annually, according to the National Institutes of Health (NIH) in the United States (https://rarediseases.info.nih.gov).[2]While forecast as a distinct entity with effects on patients, uncommon malignancies account for around 22% of all recorded instances of malignancy, including all malignancies in kids and teens. These malignancies are often under-researched and under-treated due to limited resources and a lack of awareness. Early diagnosis is key to successful treatment, and resources must be allocated to ensure uncommon malignancies are properly identified and managed. This is because the medical community often focuses on the more common forms of malignancy, such as breast, lung, and colon cancer.[3]These treatments tend to be more widely available and researched, leaving uncommon malignancies undiagnosed or underdiagnosed. By allocating resources to research and treatment of these diseases, more people can be helped, and access to treatments can be improved. It's higher than the prevalence of just one common malignancy, including carcinoma of the lungs (13%). The rates of breast cancer (16%), colorectal cancer (13%), and bladder cancer (12%).5. Because of an absence of knowledge and medical experience, rare malignancies in adults, teenage years, and children, particularly hematological tumors, are frequently misdiagnosed and incorrectly managed.[4-6] The treatment choices for uncommon malignancies are currently mostly empirical and insufficiently understood. Since these malignancies are not widely studied, there is limited data on how certain treatments will affect the patient, making it difficult for physicians to decide on the best treatment approach. Furthermore, many unknowns surround these rare cancers' genetic and molecular nuances. As a metric, prevalence captures the number of cases within a population during a specific period and is influenced by two crucial factors: incidence and survival rates. However, it can be a misleading gauge of a rarity since it fails to differentiate between infrequently occurring chronic disorders and commonly prevalent diseases with low survival rates. The study of retinoblastoma, characterized by an annual incidence of 0.35–1.18 per 100,000 individuals, has led to identifying the RB1 gene.[7] This gene, one of the pioneering tumor suppressor genes linked to hereditary cancer, was among the first to be cloned and is involved in regulating the cell cycle in the context of cancer. [8]This gene is responsible for controlling cell growth and division, and when it is mutated or absent, cells can grow and divide uncontrollably, leading to cancer. Thus, Discovering the function of the RB1 gene in cancer via studies on retinal tumours has been crucial in advancing the field of malignant tumour heredity.[9]As a result, it is critical to understand the importance of the RB1 gene in cancer, and the study of retinoblastoma can provide invaluable insights into the role of genetics in cancer.[10]

2. IDENTIFY UNCOMMON TUMOURS

Uncommon diseases encompass a broad range of conditions, including rare malignancies, which in the EU have an incidence of fewer than five instances per 100,000 people. Due to the insufficient funding for advancement of knowledge, many illnesses very frequently go undetected and pose difficult therapeutic problems. Nevertheless, with sufficient support, effective management of these conditions can be achieved through personalized treatments and preventive measures tailored to meet the unique needs of each patient. However, funding research and development for rare conditions poses its own set of obstacles, as the costs associated with developing new treatments often surpass the capacity of companies to bear. This makes it difficult for scientists and doctors to access the resources to find the best treatments for these conditions. Moreover, the uncommon diagnosis conditions is frequently challenging, primarily owing to absence of awareness and understanding surrounding these illnesses. This particular definition recognizes rare tumors as those exhibiting a prevalence of fewer than 6 cases per 100,000 individuals annually. This criterion serves as a means to gauge the level of rarity of a tumor and determine whether it falls within the category of uncommon tumors. By evaluating the annual incidence and the number of individuals affected by the tumor, it becomes possible to determine whether it qualifies as a rare or common tumor. This evaluation of the rarity of a tumour is the basis for determining whether it is uncommon. It allows researchers to accurately evaluate the impact of the tumour on a population and make the appropriate designation. It must be kept in mind that the research of uncommon tumours involves smaller categories that might be challenging to investigate in common tumors, as well as odd anatomical anomalies. Additionally, the effect of the tumor's placement, the patient's age, and its stage must be taken into account. Identifying the specific genetic changes associated with each uncommon tumour is also important. To ensure a comprehensive understanding, it is important to consider the broader clinical implications of each uncommon tumour, including its effect on the patient's overall prognosis. Understanding the myriad determinants influencing the emergence of cancer in the oral cavity is of utmost importance. Conducting a comprehensive multidisciplinary analysis of these traits holds tremendous potential in uncovering groundbreaking strategies for prevention, screening, and treatment of oral cancer. By exploring various facets, researchers can identify crucial risk factors, including tobacco and alcohol use, human papillomavirus (HPV) infection, poor oral hygiene, dietary habits, and genetic susceptibility. Furthermore, investigating the intricate interplay between these factors and their impact on molecular and cellular processes can shed light on novel therapeutic interventions. This holistic approach has the capacity to reveal targeted preventive measures, robust screening protocols, and innovative curative approaches, revolutionizing the management and prognosis of oral cancer patients. Piperine, a compound found in black pepper, has been found to inhibit the growth of oral cancer cells and may be a potential therapeutic target for oral cancer treatment. Further research is needed to understand the exact mechanism of how piperine works to inhibit cancer cell growth. Additionally, clinical trials are needed to test the efficacy of piperine as a therapeutic agent for the treatment of oral cancer. Laboratory studies have shown that piperine can induce apoptosis, or programmed cell death, in the oral cancer cells, which could potentially slow down or even stop the growth of the cancer. It has also been shown to inhibit

the growth of new blood vessels in the cancer cells, which can further reduce their growth and spread. To further understand the potential therapeutic effects of piperine, clinical trials are necessary to validate its efficacy as a treatment for oral cancer.[41,45]

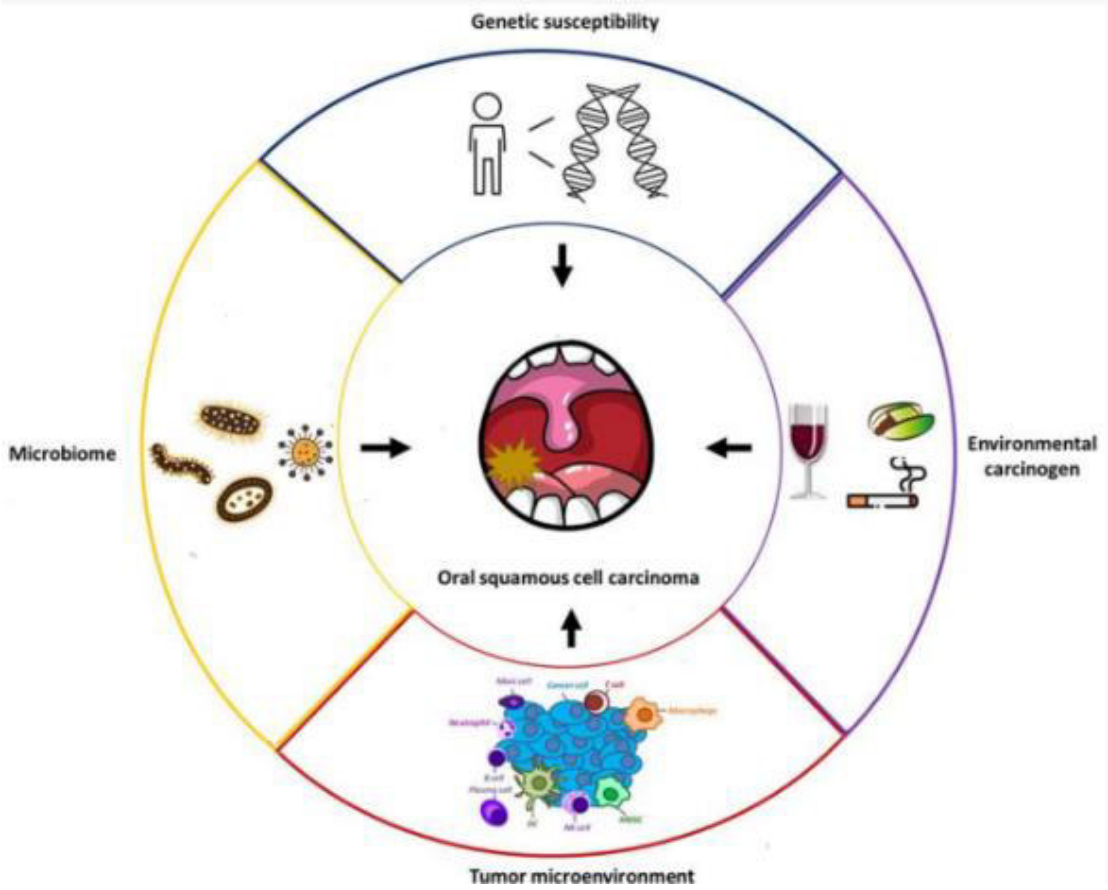

Fig 1: Important determinants of the emergence of cancer in the oral cavity. Multidisciplinary analysis of these traits might reveal novel preventive, screening, and curative findings approaches for treating oral cancer.[11]

3. DIFFICULTIES WITH UNUSUAL TUMOURS

Rare malignancies typically receive less scholarly attention and funding versus their more prevalent equivalents.[12] Besides the insufficient occurrence, individuals afflicted with rare tumors encounter distinct hurdles, including primarily inaccurate and often delayed detection, difficulties in accessing medical care and suitable treatments, a lack of trust in medical decisions, potential indifference towards the development of new medications, and a scarcity of easily accessible tumor databases and tissue repositories.[13] Biosensors for Oral Cancer Detection can enable rapid and accurate identification of oral cancer cells, allowing for quicker diagnosis and treatment, as well as potentially assisting in the development of new treatments and therapies for rare tumors. Biosensors are a relatively new technology, but they have the potential to revolutionize the diagnosis and treatment of many types of cancer. Furthermore, they offer a non-invasive method of detecting cancer that is both accurate and cost-effective. Biosensors are able to detect the presence of cancerous cells in the body, even in very early stages, by monitoring the biomarkers that indicate the presence of cancer. This can allow for early detection and treatment, which can significantly improve patient outcomes. Additionally, biosensors are relatively inexpensive and can be used in a variety of settings, including at home.[42] Difficulties with unusual tumors refer to the challenges encountered when diagnosing, treating, and managing atypical or rare types of cancerous growths in the body[14]. Their rarity characterizes unusual tumors, often deviating from the typical patterns seen in more common cancers. These tumors may have unique characteristics, behaviors, and treatment responses that pose significant hurdles for healthcare professionals[15]. Current trends for nanomaterials in cancer therapy involve the use of these tiny particles to detect, diagnose, and treat tumors in a more precise and tailored manner. Nanomaterials can also be used to increase the efficacy of chemotherapy and other treatments by delivering drugs directly to the tumor. Additionally, they can be used to help monitor the progress of the treatment and detect any recurrences of the tumor. Nanomaterials have the potential to revolutionize cancer treatments and improve patient outcomes. They offer a more precise and targeted approach to treating cancer, and can reduce the side effects associated with traditional treatments. Nanomaterials are incredibly small particles that can penetrate deep into the cells. They provide a direct delivery route for drugs, allowing for higher concentrations to be targeted directly to the tumor. This can lead to improved drug efficacy and fewer side effects. In addition, they can also be used to monitor the progress of the treatment, providing an early warning system for any recurrences.[43] One major difficulty lies in accurately identifying and diagnosing unusual tumors. Due to their rarity, healthcare providers may need more experience and familiarity with these specific types, leading to misdiagnosis or delayed diagnosis. Furthermore, specialized diagnostic tests

and expertise may be required to distinguish these tumors from more common ones.[16]Treatment can also be problematic, as the effectiveness of standard protocols may be uncertain or limited for unusual tumors. Tailoring a treatment plan requires comprehensive knowledge of the specific tumor's biology and response to different therapies. Additionally, accessing experimental or targeted treatments might be challenging due to limited availability or insufficient clinical data. Managing unusual tumors' long-term effects and potential complications can also be demanding. The rarity of these tumors means that long-term outcomes and best practices for follow-up care may need to be better understood. Ongoing research and collaboration among healthcare professionals and support from patient advocacy groups are crucial in addressing the difficulties associated with these rare and unusual tumors.[17]

4. DIFFICULTIES WITH STRANGE TUMOUR DETECTION

Histopathological examination is a crucial step in evaluating rare cancers and plays a vital role in determining suitable treatment approaches. Nevertheless, this process carries a notable risk of interpretational errors, with rates ranging from 25 to 40 percent in routine clinical practice. The subjective nature of histopathology, where the interpretation of slides depends on the expertise of the pathologist, contributes to this challenge.[18,19] Moreover, there needs to be more standardization in the analysis process, which can lead to misdiagnosis and inappropriate treatments. However, this risk of misinterpretation is a serious concern and should not be overlooked, as it could result in inaccurate diagnoses and inappropriate treatments. While tissue diagnosis remains a crucial aspect of cancer management, it is important to acknowledge the potential for interpretational discrepancies in evaluating rare cancers.[20] Diagnostic accuracy in rare cancers can be influenced by several crucial factors, including subjective judgment and limited expertise among specialists, variability in observations within and between observers, and inadequate tumor samples submitted for examination. It is imperative to urgently expand methodologies aimed at enhancing diagnostic accuracy. By adopting this approach, we can effectively minimize errors in interpretation and, consequently, enhance the capacity to find suitable treatments for people with uncommon malignancies. Patients with rare tumours can benefit from increased survival rates and greater quality of life by improving diagnosis accuracy and putting in place suitable treatment strategies. The outcome is, this approach enables the healthcare system to maintain reasonable expenditure levels.[21,22]

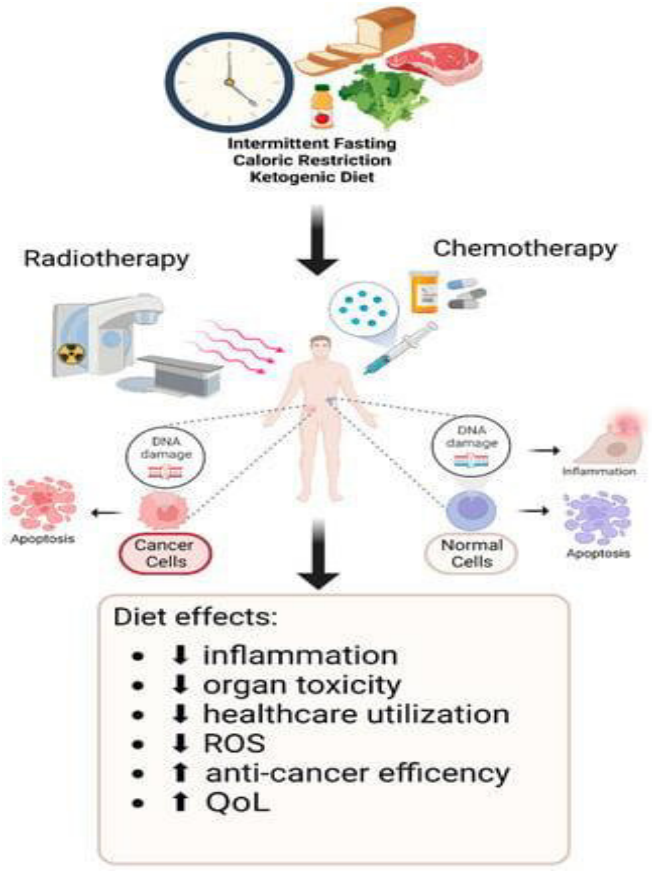

Fig 2: Potentially beneficial benefits of food modifications on cancer clients.[23]

5. PROBLEMS WITH THE TREATMENT OF UNCOMMON MALIGNANCIES

Although there have been improvements in the management of uncommon tumours, there are still many difficulties for physicians to overcome. It is crucial to emphasise the relevance of uncommon malignancies of the genitourinary (GU) tract because they provide as an excellent example of the challenges doctors face in their treatment. [24] It is challenging to develop a clear plan based only on existing recommendations reinforced by considerable research since there is a dearth of recognised therapies for uncommon malignancies and a limited supply of clinical information on these diseases. Therapists typically lack a clear strategy to meet the specific requirements for clients with uncommon tumours due to a lack of accessible studies and medical

criteria. It is critical to understand that different patients may respond differently to a certain course of medical care for a specific tumour. In such circumstances, useful knowledge gained from early-phase research and clinical trials plays a key role in directing therapy choices. Clinical studies can also produce theories for prospective treatments designed particularly for uncommon tumours. Investigating the fundamental processes behind the onset of these uncommon malignancies through laboratory research and translational studies is another path worth taking.[25] This dual approach, Integrating experimental studies with experimental treatments can offer crucial insights into the management and therapy of uncommon tumours. The table below illustrates the annual occurrences of both common and uncommon malignancies.

Table 1: Annual occurrences of a few common and unusual malignancies [26.]

Cancer Type	RARECARE incidence	CINA incidence	Common cancers
Prostate	47.89	215.65	
Breast	63.85	96.18	
Lung	55.93	85.49	
Colon	42.64	53.49	
Uterus	10.40	32.06	
Bladder	20.11	29.95	
Rectum	17.11	20.30	
Ovary	9.39	17.99	
Kidney	10.55	15.81	
Melanoma	48.58	21.26	
Non-Hodgkin lymphoma	17.45	17.36	
Stomach	15.23	10.43	
Fibrolamellar hepatocellular	0.01	-	IRCI-selected rare cancers
Gynecological sarcoma	0.50	-	IRCI-selected rare cancers
Thymoma	0.13	-	IRCI-selected rare cancers
Metastatic anal cancer	1.09	1.92	IRCI-selected rare cancers
Penile cancer	0.62	0.12	IRCI-selected rare cancers
Small bowel adenocarcinoma	0.72	2.31	IRCI-selected rare cancers
Salivary gland cancer	0.73	1.61	IRCI-selected rare cancers
Ocular melanoma	0.65	-	IRCI-selected rare cancers
Anaplastic thyroid cancer	0.17	-	IRCI-selected rare cancers
Rare brain cancer	0.78	-	IRCI-selected rare cancers

IRCI=International Rare Cancers Initiative.;CINA=Cancer in North America.

6. INTERNATIONAL RARE CANCERS INITIATIVE (IRCI)

International clinical trials for uncommon malignancies can be carried out if there is sufficient financing, organising, and backing to create treatment options.[27,28] To tackle this problem and promote the extension of international trials for uncommon tumours, the IRCI was created at its inception of 2011. The National Cancer Institute (NCI), Cancer Research UK (CR-UK), the European Organisation for Research and Treatment of Cancer (EORTC), and the National Cancer Institute (NCI) have partnered to develop IRCI.[29,30] The IRCI's mission is to support global study designs for uncommon cancers to advance the development of novel treatments for these conditions. To achieve this mission, the IRCI works to promote early diagnostics and the implementation of precision medicine practices, as well as to create a global network of researchers and clinicians focused on uncommon cancers. This global network will enable the sharing of research, clinical data, and best practices related to uncommon cancers, facilitating the development of targeted treatments for these conditions. Additionally, the IRCI works to increase public awareness of uncommon cancers and to advocate for improved access to care for patients. By doing this, the IRCI hopes to lead to better outcomes for patients with uncommon cancers, as well as to strengthen the global network of cancer researchers and clinicians. This will allow for better collaboration and help accelerate the development of treatments for these cancers.[44] Additionally, it allows affiliate teams to debate clinical trials for malignancies that wouldn't otherwise have access to worldwide organising infrastructure, organise discussions on universal rare disease policy, and support affiliate organisations in evaluating concepts and practices. To debate and create potential research suggestions, IRCI arranges in-person meetings and teleconferences. Creating connections with businesses is another important goal. These meetings aim to discuss potential research topics that interest the business and develop relationships with key individuals in the business.[31]By having these connections, IRCI can better understand the needs of the business and develop research proposals that will meet their needs. Additionally, having these conversations allows IRCI to build trust with the business, proving their research is reliable and trustworthy.

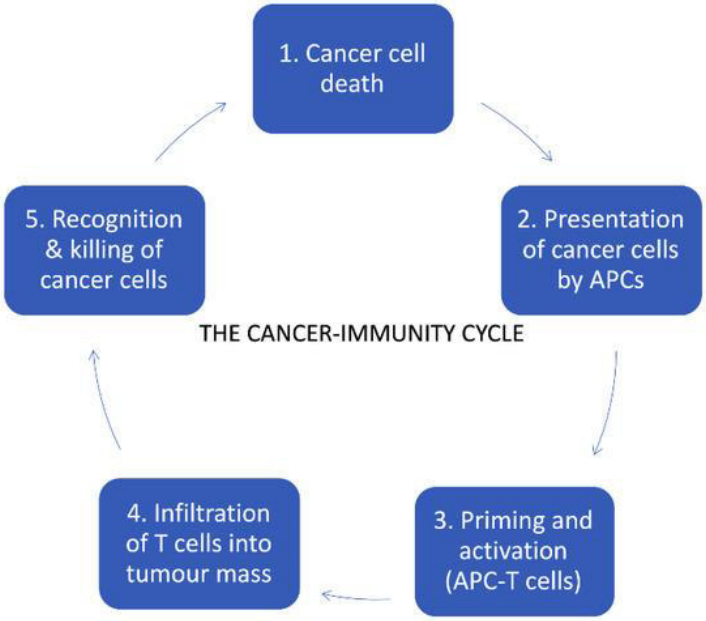

Fig 3: The cycle of cancer immunity[32]

7. ADVANCING TREATMENTS FOR UNCOMMON CANCERS

Determining several structurally specified uncommon malignancies has been made possible by advancements in cancer biology and genomic gadgets, simultaneously changing the approach and methodology of medication discovery. Identifying genetic changes in uncommon tumours can aid in prognosis and serve as a possible target for therapeutic intervention.[33,34] However, the fast evolution of diagnosis concepts makes it challenging to consistently identify cases and muddles efforts at systematically gathering data. Due to the development of antibodies, genetic subclassification can be expanded to incorporate maintain variables like immunological antigen activation and tissue infiltrates. Numerous uncommon malignancies, including adolescent granulosa and small-cell malignancies of the ovarian hypercalcaemic type, have modest mutational loads and appear to trigger little in the way of host immune responses.[35] Although the use of immunotherapy in treating uncommon tumours has initially shown some promise, its full potential is yet unknown. Regardless of whether the driver mutation is present in a rare or prevalent cancer, creating medications based on these variants is still significant since many of these therapies can be reused. The use of immunotherapy has the potential to be used to treat a wide variety of cancers, regardless of the type of mutation present.[36] By targeting the driver mutation, it can be used to create personalized treatments tailored to the patient's specific needs. Additionally, the medications produced through the immunotherapy process can be reused to treat different cancers, making them much More cost-effective in the long run. Furthermore, this approach has been shown to have greater efficacy than traditional treatments, making immunotherapy an increasingly attractive option for cancer treatment.

8. EXPERIMENTAL STUDIES USING RANDOMIZATION FOR UNCOMMON MALIGNANCY

Experimental studies employing randomization for uncommon malignancies have emerged as an integral approach in oncology research. These studies play a pivotal role in investigating the effectiveness of various interventions, treatments, or therapies for rare forms of cancer that have limited available data due to their infrequency. Randomization, a fundamental principle in experimental design, ensures equitable allocation of participants to different study groups.[37]researchers can minimize selection bias and establish a more reliable cause-and-effect relationship between the intervention and outcomes by randomly assigning individuals to treatment and control groups. Randomized studies become even more valuable for uncommon malignancies, where conventional clinical trials may be challenging due to low patient numbers. These studies provide a structured framework to evaluate new therapeutic strategies, such as novel drugs, targeted therapies, immunotherapies, or combinations thereof, rigorously and systematically. [38]Through randomized experimental studies, researchers can gather evidence on treatment efficacy, safety profiles, potential side effects, and long-term outcomes specific to uncommon malignancies. This knowledge is essential for influencing therapy recommendations, supporting medical judgement, and enhancing patient outcomes in these uncommon tumour forms. Periodontal therapy is the cornerstone of treatment for these tumours, and knowledge of their molecular characteristics is vital for determining the appropriate medical and surgical interventions. Understanding the molecular characteristics of these tumours will help clinicians to choose the best treatment options for each patient, and to understand the risks and benefits of each treatment. This will ensure the best possible outcome for patients with these kinds of tumours. By studying the molecular characteristics of these tumours, clinicians are able to better understand how the tumour is likely to respond to various treatments. This can help them to decide on the best course of action, as well as identify potential risks and side effects. This can ultimately lead to better outcomes for patients with these tumours.[46] Focused genetic treatment, commonly called biological medicine, has significantly advanced several uncommon cancers[39]. Furthermore, collaborative efforts among research institutions, oncologists, and patient advocacy groups play a significant role in facilitating the enrollment of participants in

these studies. These collaborations enhance randomized experiments' feasibility and statistical power for uncommon malignancies by pooling resources and expertise. In summary, experimental studies utilizing randomization provide a robust and scientific approach to investigating interventions for uncommon malignancies.[40]These studies are essential for generating evidence-based knowledge, expanding treatment options, and advancing the field of oncology to address the needs of patients with rare cancers. Bio-based materials, such as stem cells, gene-editing, and immunotherapies, are being used to develop treatments for rare cancers and chronic diabetic conditions. With the help of these studies, researchers can identify the molecular pathways responsible for cancer and develop new drugs and treatments. Additionally, these studies can provide insight into how to better target and personalize treatments for individual patients, allowing for more tailored and effective care. Furthermore, this research can also be used to create personalized diagnostics and therapies, increasing the efficacy of treatments and improving patient outcomes.[47]

9. CONCLUSION

Due to its small occurrence, rare malignancies have yet to be the subject of much research. Because of this, determining undeniable aetiological risk variables might be challenging for statistical investigations. Furthermore, different countries may have different rates of rare cancers. Given the diversity of the citizenry, India may have an abundance of people with uncommon cancers. The production requires contributions from several other nations. Consequently, there remains a lot of work to be done. Improved multicentric research on uncommon malignancies can help with diagnosis, therapy, and forecasting, leading to important discoveries regarding cancer biology. However, conversion must be done cautiously and with preliminary tests in the proper model organisms. When knowledge expands, it will be essential to keep in mind that acceptance of DNA subclassification depends on its actual usefulness. Cell environment must be taken into account when applying particular treatments developed for typical cancers to the rare situation. Improved possibilities for therapy for individuals with unusual cancers should result from investigators collaborating to develop conventional approaches to evaluate studies that acknowledge the difficulties in conducting trials in rare cancer settings and provide ways to capture results for patients shortly after authorization.

10. AUTHORS CONTRIBUTION STATEMENT

All authors have made a substantial, direct, and intellectual contribution to the work and approved it for publication. Dr. Somnath Gosh contributed to the data extraction, analysis, and article preparation. Bhuminathan.S, Lakshmi K, M.Vinyas, Pavithraanand Ammayappan and SelvaKumar contributed by being a part of writing the article.

11. CONFLICT OF INTEREST

Conflict of interest declared none.

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