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Review Article

The future of pediatric oncology: Comprehensive review of causes, mortality, and treatment strategies

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Abstract

Pediatric oncology is confronting rising cancer rates among children, which poses a significant global health challenge. This review article delves into the multifaceted aspects of pediatric cancers, including their etiology, advanced diagnostic methods, and comprehensive treatment approaches. The article explores both genetic predispositions and environmental factors that contribute to the development of cancer in children. It underscores the importance of cutting-edge diagnostic tools such as next-generation sequencing and liquid biopsies. These technologies have revolutionized our understanding of cancer's molecular basis, leading to more precise diagnoses and enabling personalized treatment regimens. In terms of treatment, the review discusses traditional methods like chemotherapy, radiation therapy, immunotherapy, target therapy, stem cell transplant and surgical interventions. It also sheds light on innovative therapies such as immunotherapy and targeted treatments that have shown promise in improving survival rates while minimizing adverse effects. The review also addresses the stark disparities in healthcare access and survival rates between developed and developing countries. It emphasizes the critical need for global efforts to provide equitable care to all pediatric cancer patients. Looking ahead, the article highlights the potential of personalized medicine to transform pediatric oncology. It also points to emerging therapies and international collaborations as key factors in advancing care and outcomes for young patients with cancer. This comprehensive review serves as a valuable resource for healthcare professionals, researchers, and policymakers. It provides a thorough analysis of current challenges in pediatric oncology and offers a forward-looking perspective on opportunities for future advancements.

Keywords: Pediatric oncology; Mortality ratio; Chemotherapy; Immunotherapy; Challenges; Future strategies

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INTRODUCTION

Precision oncology is gaining traction as an innovative strategy in pediatric cancer treatment, focusing on tailoring therapies to the unique genetic profiles of individual tumors. This method holds significant promise for revolutionizing childhood cancer care by delivering more effective and targeted treatments[1]. The application of genome-informed targeted therapy in osteosarcoma underscores the critical role of understanding genetic alterations in tumors. This knowledge is essential for guiding treatment choices and improving patient outcomes[2-5]. Chromatin remodeling has been recognized as a crucial element in the development of pediatric brain tumors, with genes such as SMARCB1 being particularly influential. Gaining

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insight into these molecular mechanisms paves the way for targeted therapies that could enhance treatment efficacy[6,7]. Furthermore, zebrafish models have been employed to investigate pediatric brain tumors, providing important insights into the biology of these cancers. In pediatric oncology, psychosocial interventions are vital for addressing the emotional and psychological needs of young cancer patients[8]. Personalized interventions have been shown to significantly improve outcomes and elevate the quality of life for children undergoing cancer treatment[9]. Moreover, palliative care is a critical element of pediatric oncology, ensuring that children with cancer receive thorough support and comfort throughout their experience[10]. Pediatric oncology is an essential branch of medicine focused on diagnosing and treating cancer in children. This field addresses a range of childhood cancers, including brain and central nervous system tumors, bone neoplasms such as osteosarcoma, and hematological malignancies like acute myeloid leukemia and lymphomas. These conditions pose a significant global health challenge. The treatment of pediatric cancer involves various advanced technologies designed to enhance outcomes and reduce side effects in young patients. Radiotherapy has notably progressed, incorporating photon and proton therapy, image-guided patient positioning, motion management, and adaptive therapy[11,12]. These advancements are pivotal in effectively treating children with cancer. Proton beam radiotherapy, especially, is being increasingly provided to children and young people, offering a more precise treatment with fewer side effects. Immunotherapy, notably CAR T cell therapy, has also emerged as a promising method in pediatric oncology, particularly for brain tumors. These cutting-edge therapy targets specific antigens on cancer cells, offering a personalized and targeted treatment approach that holds potential for improving survival rates and enhancing the quality of life for pediatric patients[13,14]. Positron emission tomography-computed tomography (PET-CT) plays a crucial role in pediatric oncology by assisting in neoplasm staging and treatment planning. As PET-CT availability has increased, it has been seamlessly integrated into various pathways for pediatric cancer patients, leading to improved accuracy in diagnoses and treatment monitoring[15]. In the realm of pediatric oncology, there is growing interest in designing pharmaceutical care models specifically tailored to enhance the quality of care for young cancer patients. Researchers and practitioners are actively developing innovative tools and approaches to empower pharmacists in creating world-class care models that address the unique requirements of pediatric oncology patients. The ultimate goal is to improve treatment outcomes and enhance the overall patient experience[16].

Amidst the COVID-19 pandemic, providing pediatric cancer care has faced significant hurdles. These include surgical procedure disruptions, chemotherapy adjustments, and radiotherapy interruptions. As a result, adaptations have been crucial to maintain uninterrupted treatment for young oncology patients[17].

This review article delves into pediatric oncology, elucidating the causes, diagnostic approaches, treatment modalities, challenges, and future prospects. It explores the genetic and environmental factors contributing to pediatric cancers, highlighting the latest diagnostic technologies such as next-generation sequencing and liquid biopsies. Treatment strategies are examined, including chemotherapy, radiation, surgery, and advanced therapies like immunotherapy and targeted treatments. The article addresses the multifaceted challenges in pediatric oncology, from healthcare access disparities to economic and social barriers. Looking forward, it discusses innovations in personalized medicine, emerging therapies, and global collaborative efforts to improve outcomes and care for young cancer patients.

2. CAUSES OF PAEDIATRIC ONCOLOGY

Pediatric oncology is a medical specialty dedicated to diagnosing and treating cancer in children. It addresses various cancers that affect young patients. Genetic factors are crucial in determining a child's risk of developing cancer[18]. Research has shown that unique genetic variations and inheritance patterns outside the traditional Mendelian framework can impact this risk. In-depth genomic studies have pinpointed key mutations in genes such as ALK, NF1, and PTEN in solid tumors, and mutations in FLT3, PIK3CA, and RAS genes are commonly found in leukemias[19,20]. These mutations can disrupt essential cellular pathways controlling growth and division, leading to the development of cancer.

In the field of pediatric oncology, inherited genetic changes are key factors that can make children more susceptible to cancer. Unlike cancers in adults, which typically have many somatic mutations, childhood cancers tend to have fewer of these mutations but a greater number of inherited (germline) changes in genes known to increase cancer risk[21]. These inherited mutations are found in genes linked to a variety of solid tumors in children, including medulloblastoma, ependymoma, neuroblastoma, retinoblastoma, Wilms tumor, osteosarcoma, rhabdomyosarcoma, and Ewing sarcoma[22]. When these genes are mutated, they can disrupt normal cell functions related to growth and development, thus heightening the risk of cancer in young individuals[23]. Research indicates that inherited genetic changes could be responsible for up to 10% of cancers in children. For example, hereditary retinoblastoma is often linked to inherited mutations in the RB1 gene, with about 40% of these eye cancers being hereditary[24]. Moreover, genetic conditions such as Li-Fraumeni syndrome, which results from inherited TP53 mutations, are known to significantly raise the risk of various pediatric cancers, including acute lymphocytic leukemia[25]. The rise of cutting-edge genomic tools, such as next-generation sequencing, has revolutionized our ability to uncover the genetic roots of inherited cancer syndromes in children[26]. These advanced methods have made it possible to spot rare genetic changes that lead to the loss of function in genes, like ELP1, and have highlighted their role in increasing the risk for certain childhood cancers, including medulloblastoma[27]. Genetic counseling and testing are now crucial in caring for young oncology patients who may have inherited cancer syndromes[28]. By pinpointing children with inherited mutations in genes linked to cancer, medical professionals can design

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personalized monitoring and preventive strategies[29]. This tailored approach highlights the significance of genetic insights in pediatric oncology, aiming to enhance patient outcomes and provide specific care for those at heightened risk. Environmental influences are significant in the field of pediatric oncology. Beyond genetic factors, children's exposure to elements like ultraviolet rays, ionizing radiation, and certain cancer treatment drugs can contribute to the emergence of cancer. Research, including findings by Rodríguez-Galindo et al. in 2015, suggests that these environmental exposures may act alongside genetic vulnerabilities to trigger and advance cancer in young patients[20,30]. Other environmental factors, like ionizing radiation and chemotherapy drugs, can also affect how often cancer occurs in children[31]. These environmental risks may combine with genetic vulnerabilities to further elevate a child's chances of developing cancer. Beyond the direct risk of cancer, environmental elements also affect life quality and the success of treatments in pediatric oncology. The widespread impact of cancer and its treatments has shifted attention towards supportive care and rehabilitation, aiming to improve both the physical and emotional health of children in treatment[32]. Additionally, a child's nutritional status emerges as a pivotal environmental factor that can shape their response to treatment, their ability to tolerate therapy, and ultimately, their chances of survival[33]. The healthcare setting plays a critical role in the delivery of pediatric oncology care. The availability of specialized services, the presence of healthcare inequalities, and access to skilled professionals all shape the standard of care that children with cancer receive[34]. Furthermore, the working conditions for healthcare workers, particularly pediatric oncology nurses, have a profound impact on their job satisfaction and the quality of care they provide to young cancer patients[35]. Within pediatric oncology, the COVID-19 pandemic has brought about new environmental hurdles, such as delays in treatment and disruptions in healthcare services, which could affect the progression and outcomes of diseases[36,37]. Tackling these added stressors calls for a collaborative, multidisciplinary strategy that addresses the specific needs of young cancer patients and strives to maintain high-quality care amidst these external obstacles.

Treating cancer in children, a key focus of pediatric oncology, often involves chemotherapy. Chemotherapy stands as a cornerstone in treating childhood cancers, employing drugs like anthracyclines, alkylating agents, and antimetabolites that are known to damage DNA and interfere with cell division in cancer cells. Yet, these powerful medications can also affect normal tissues and organs, leading to a range of side effects in young patients[38,39]. Anthracyclines, a class of drugs commonly used in treating childhood cancers, are associated with heart-related toxicities, which can manifest as heart failure or cardiac dysfunction in some patients[40]. Additionally, there's a concern for secondary cancers, such as therapy-related myeloid neoplasms, following chemotherapy[41]. These secondary conditions are thought to arise from the damaging effects of chemotherapy on the blood-forming stem cells, potentially leading to leukemia or myelodysplastic syndromes[41]. Chemotherapy can also affect the brain and nervous system in young patients, leading to neurotoxicity and learning difficulties. Studies have shown that these drugs can cause brain damage through mechanisms that lead to excessive neuron activation and cell death, resulting in physical changes in the brain and cognitive challenges for children undergoing cancer treatment[42]. Moreover, chemotherapy's role in pediatric oncology has been linked to a heightened risk of developing secondary conditions like therapy-related myelodysplastic syndrome or acute myeloid leukemia, highlighting the potential long-term impacts of chemotherapy in children[43]. Chemotherapy doesn't just attack cancer; it can also weaken the body's defenses, making children more prone to catching infections, even serious ones like septicemia[44]. Since their immune systems are already under attack, it's crucial to keep a close eye and provide extra care to prevent and treat these infections. While chemotherapy is a powerful tool against cancer in kids, it's not without its downsides and potential long-term issues. That's why it's so important to tailor treatments to each child and support them through the process. Doctors aim to strike a balance, getting the most out of chemotherapy while keeping its negative effects to a minimum for the best possible results.

This highlights the critical need for incorporating pharmacogenomics the study of how genes affect a person's response to drugs into pediatric cancer care. Doing so aims to improve treatment effectiveness and reduce the likelihood of harmful side effects. In pediatric oncology, care for young cancer patients goes beyond medical treatment to include palliative care for those with serious, life-threatening conditions. This type of care focuses on providing comprehensive support to children and their families from diagnosis onward, prioritizing comfort and quality of life while managing symptoms[45]. It acknowledges the distinct needs of these young patients and underscores the value of a team-based approach that covers the full spectrum of physical, emotional, and social needs.

3. MORTALITY RATIO OF PEDIATRIC ONCOLOGY

Children battling cancer face a particularly tough journey, especially when they require intensive care. When these young warriors are admitted to the Pediatric Intensive Care Unit (PICU), their risk of not making it is significantly higher than other children in the PICU[46]. In fact, while only 2% to 5% of all kids in the PICU may sadly pass away, this number jumps to 7% to 15% for those fighting cancer. And although they make up just over 4.2 % of those admitted to the PICU, these brave little fighters account for more than 11.4 % of the deaths there. It's a sobering reminder of the courage they show every day[47]. The delicate health of children with cancer is further compromised by several factors that raise their risk of mortality. For example, when these children need help breathing due to heart complications and are put on mechanical ventilation, their chances of survival decrease more so than even those who have undergone transplants[48]. In fact, the likelihood of passing away for these young cancer patients on ventilators is alarmingly high, with an odds ratio of 18.49[49]. Sepsis, a severe infection, also poses a significant

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threat, as its 1.6 times more likely to be fatal for these children compared to other pediatric patients[50]. Boosting survival rates for children with cancer in the PICU remains a multifaceted task. Thankfully, advancements in intensive care have led to a decrease in mortality rates among these critically ill young patients, yet there's still much progress to be made[51]. Crafting specialized care plans and implementing systems that can quickly spot when a child's condition is worsening are key to bettering their chances and lowering the number of lives lost[46,47]. In essence, children with cancer, especially those needing PICU care, face greater survival challenges than other kids. The necessity for mechanical ventilation, severe infections like sepsis, and particular cancer-related health issues all add to their heightened risk. To turn the tide, it's vital to refine our care strategies, enhance early detection, and embrace a team-based approach to nurture these young patients towards recovery. The different observed cases of pediatric oncology in USA in 2014[52] are summarized in Figure 1.

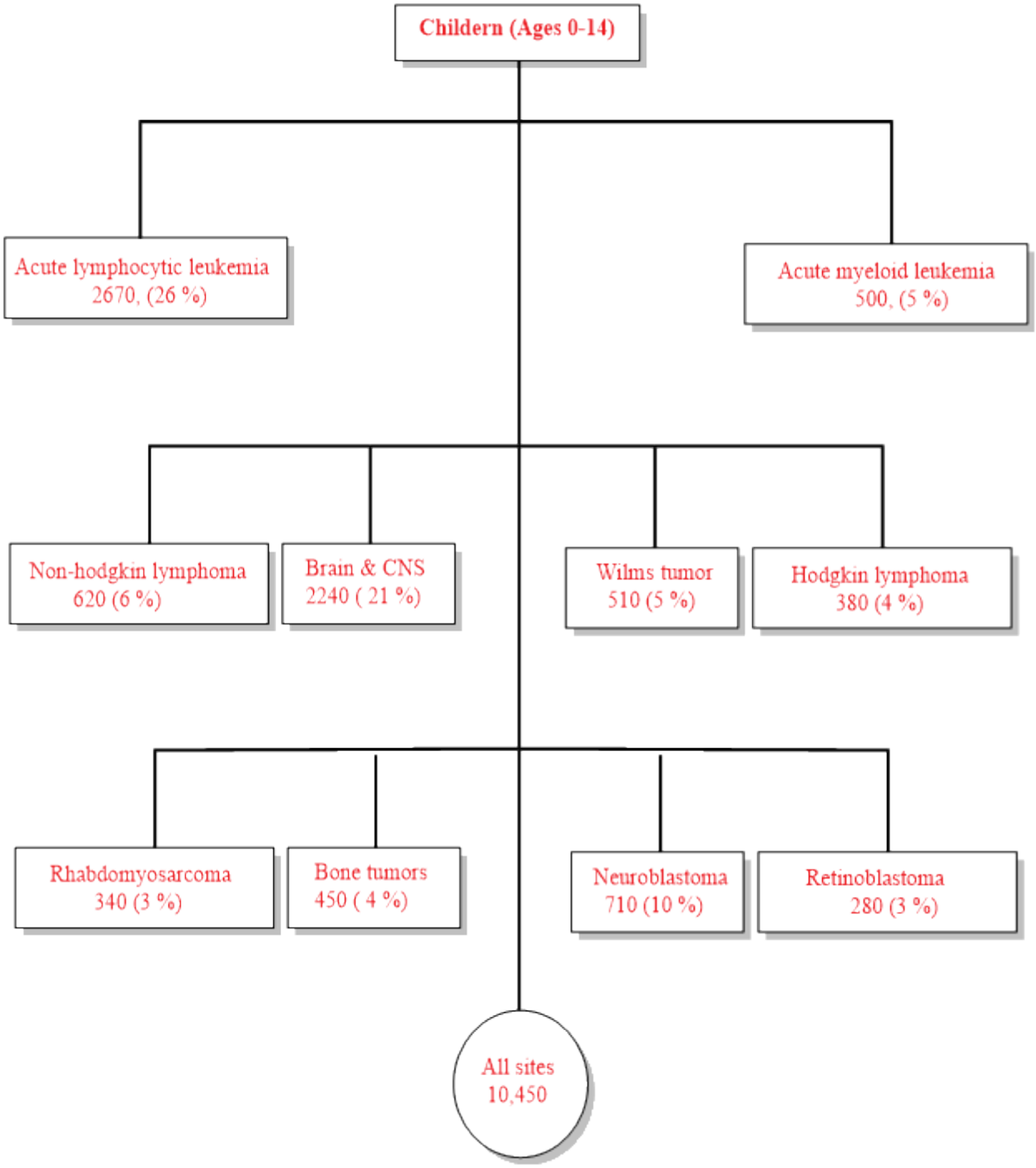

Figure 1. Flow sheet diagram for the pediatric oncology cases observed in USA

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4. DIAGNOSTIC METHODS

Figure 2 illustrates the most common diagnostic methods in pediatric oncology: radiography and fluoroscopy, ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI). These imaging techniques are essential for detecting, staging, and monitoring tumors in children.

4.1 Radiography and Fluoroscopy

In the realm of medical imaging, 'radiography' is often used interchangeably with 'X-ray', a term familiar even among radiologists. The core components of both fluoroscopy and radiography are an X-ray tube and a detector. Previously, imaging relied on film detectors, but now, digital technology reigns in the U.S. and other developed nations, offering immediate access to images worldwide a stark improvement over film, which could be lost or require retakes. Remarkably, radiography has become 95% safer since the 1950s due to enhanced detector efficiency[53]. While pediatric fluoroscopy presents unique challenges, innovations have led to more efficient systems, reduced frame rates for less radiation exposure, and features like 'last image store' for extended review without continuous radiation. Radiography remains a staple in pediatric imaging, accounting for two-thirds of all scans. It's often the first step in detecting cancer in children, leading to more detailed follow-up tests like MRI or CT scans based on initial X-ray results. Radiography's role varies depending on specific cancer protocols; for instance, chest X-rays for lung metastasis are increasingly replaced by chest CTs. For widespread skeletal conditions, whole-body MRI and PET scans are becoming more common due to their superior sensitivity[54-57]. Yet, radiography still plays a crucial role in urgent situations like infections or obstructions in immuno-compromised children.

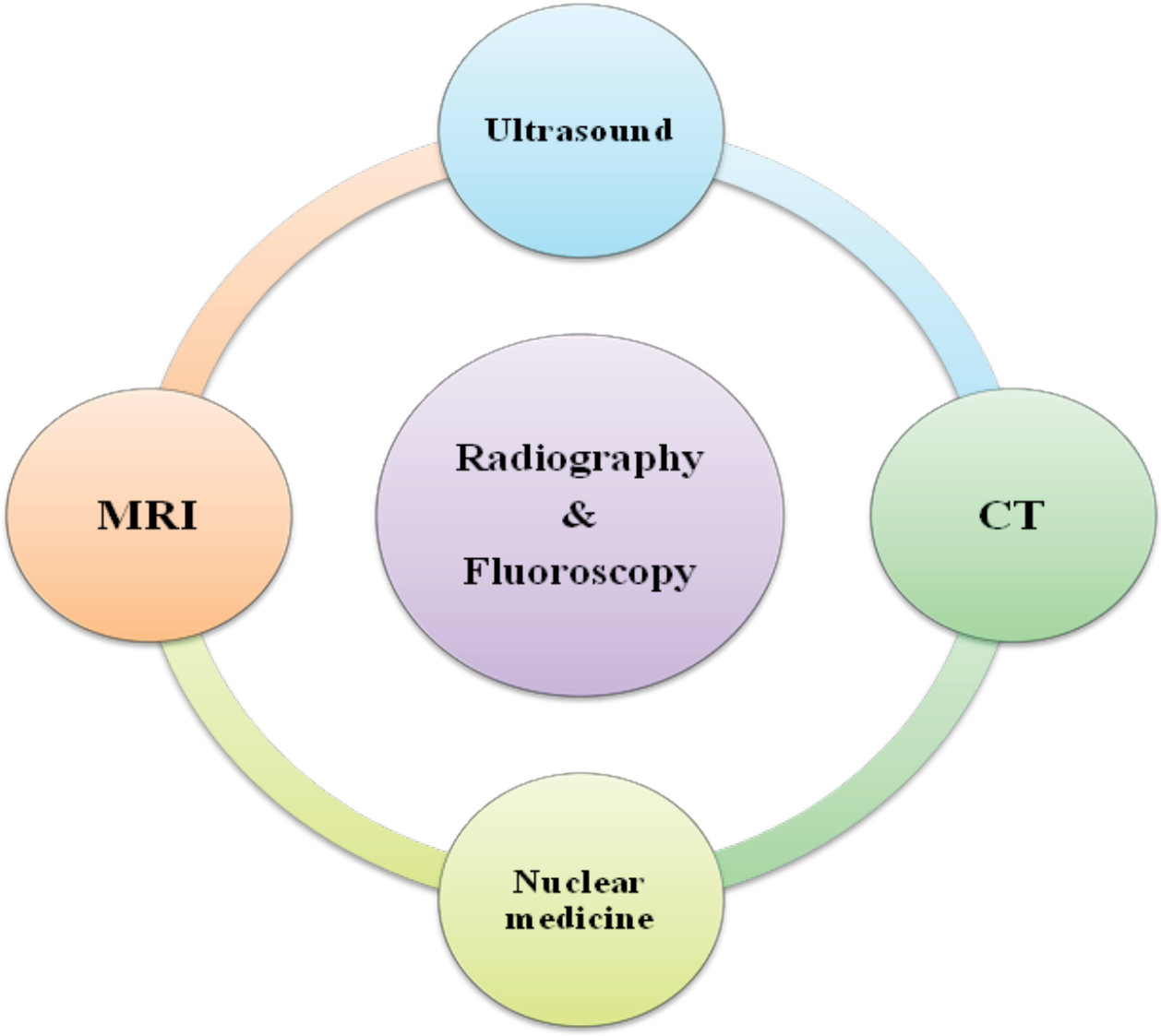

Figure 2. Different diagnostics techniques for detection of pediatric oncology.

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Fluoroscopy's use in cancer evaluation is minimal but can reveal unexpected findings during routine checks. It's also useful for post-surgical assessments and device placements. The primary safety concern with these imaging techniques is radiation exposure, which remains quite low for most radiographic procedures[58,59]. A chest X-ray exposes a child to the same amount of radiation they'd encounter naturally over two days. For specific scans, like a foot X-ray in Ewing sarcoma cases, the radiation is even less equivalent to just 40 minutes of everyday exposure. Modern fluoroscopy doses are generally low, depending on the procedure. In the grand scheme of things, radiography and fluoroscopy contribute only 6% and 3%, respectively, to a child's annual radiation dose in the U.S., while CT scans account for a hefty 84% due to their higher radiation levels per exam. Nuclear imaging and interventional procedures each add another 3% and 4%[60]. When it comes to contrast agents used in imaging, those taken orally or through catheters are safer than intravenous ones. Barium, an inert contrast medium, rarely causes reactions. Yet, iodinated agents are preferred if there's a risk of leaks into the body's cavities since barium can linger for years, potentially causing complications like bowel obstruction though this risk is now questioned[61]. Radiography and fluoroscopy stand out for their accessibility, portability (with devices like 'c-arms' for fluoroscopy), and cost-effectiveness compared to other imaging methods. They're also consistently performed, with some variation in fluoroscopy due to operator skill levels. Unlike CT or MRI scans, radiography doesn't require children to stay still a boon for squirmy preschoolers as any movement is immediately noticeable and easily managed by simply waiting for a calm moment to proceed.

4.2 Ultrasound

Ultrasound is an indispensable tool in caring for children with cancer. It serves many roles, from sizing up tumors and tracking how well treatments are working to aiding in procedures and spotting any treatment-related issues. This gentle imaging technique is especially suited for young patients because it doesn't use harmful radiation, so it's safe for frequent checks, and it gives doctors a live view into the body's inner workings. Research underscores ultrasound's pivotal role in child cancer care. For example, it's proven reliable for identifying skull fractures, showcasing its utility right at the patient's bedside[62]. Ultrasound has also shown promise in aiding spinal taps for overweight children with cancer, further proving its adaptability in supporting various medical procedures[63]. Studies have explored how safe it is to use ultrasound contrast agents in children with cancer. These studies, which include kids with solid tumors in clinical trials, show that using contrast-enhanced ultrasound (CEUS) could improve how well we can diagnose these young patients[64]. In the specialized field of brain cancer treatment in children, using ultrasound during surgery is proving to be incredibly helpful. This tool, combined with cutting-edge MRI and surgical navigation, helps doctors plan and perform surgeries better[65]. It allows them to see tumors clearly and know exactly how much to remove, leading to better surgery results for kids with brain tumors. Ultrasound is a key imaging method in child cancer care because it's safe, shows images in real time, and doesn't hurt the patient. As ultrasound technology gets even better, it's expected to greatly improve the care and outcomes for young cancer patients.

4.3 Computed Tomography

Computed tomography (CT) scans are crucial in managing cancer in children. They not only provide precise details and consistent tracking of the disease's location and nature but also help in overseeing the effectiveness of cancer treatments. Moreover, CT scans are instrumental in spotting both immediate and long-term side effects of cancer and its treatments, as well as in detecting any recurrence of the disease[66]. While there are concerns about the ionizing radiation used in CT scans, the potential hazards are considered very small. Generally, the immediate health benefits of a necessary CT scan greatly surpass any potential risks. It's important to weigh the immediate advantages of a CT scan against the uncertainties of other diagnostic methods, more invasive procedures, or choosing not to use diagnostic imaging at all[67]. One of the key strengths of CT scans in imaging for child cancer care is the quickness with which images can be taken. This speed has greatly improved since the early days of CT in the 1970s and 1980s. Today's CT machines can capture images in just a few seconds, reducing blurriness caused by breathing or small movements. CT scans are also very adaptable and provide reliable, repeatable results, making them ideal for keeping an eye on children with cancer[68]. They are widely used because they are fast, consistent, and give high-quality information[69]. While this review focuses on CT scans, other imaging methods and their important roles in child cancer care are also well-documented in medical research[70]. For accurate diagnosis in CT scans of the neck, chest, and abdomen-pelvis in children with cancer, using intravenous iodine-based contrast media is almost always essential. The main exceptions are brain tumors and bone or muscle imaging, where MRI is usually preferred. While modern CT scanners don't always require a contrast agent for abdominal scans, many medical centers still recommend it[71]. Children have fewer reactions to contrast agents than adults, but it's still something doctors consider. Also, there's growing concern about how these contrast agents might affect the thyroid function in young children[72,73]. Photon-counting CT is a cutting-edge technology that uses advanced detectors to identify the energy of each X-ray photon, unlike traditional CT that averages out many photons[74]. This innovation leads to clearer images with better contrast and resolution, as well as improved color imaging. For children with cancer, photon-counting CT could reduce radiation exposure, provide higher quality images, make better use of contrast agents, and give radiologists new types of valuable information.

4.4 Magnetic Resonance Imaging (MRI)

MRI is an essential tool in detecting and treating cancer in children. It's invaluable for diagnosing, determining the stage of cancer, planning treatment, and tracking how well treatment is working. MRI stands out because it's non-invasive and doesn't use ionizing radiation, which is especially important for children who need regular check-ups over time[75]. Whole-body MRI is becoming a key imaging choice in child cancer

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care, as it avoids the ionizing radiation that comes with CT and PET scans. This is particularly beneficial for children who need many scans to track their illness. Techniques like diffusion-weighted imaging and Dixon-based imaging within whole-body MRI are proving to be valuable, offering detailed insights into the body's conditions[76]. In treating brain tumors in children, advanced MRI methods like functional MRI and diffusion tensor imaging have made a big difference. They help surgeons plan operations, navigate during surgery, see tumors clearly, and decide how much to remove. These improvements have led to better surgery results for these young patients[77]. MRI is also key in assessing tumors in children, not just for cancer but also for other conditions like eye socket tumors. Its ability to show the exact location, size, and impact on nearby structures is vital for making the right diagnosis and treatment plan[78].

4.5 Nuclear Medicine

Nuclear medicine is a pivotal part of child cancer care. It uses special drugs and imaging to look into the body's functions and tiny molecular changes, helping to find, describe, and treat different types of childhood cancers. In child cancer treatment, nuclear medicine techniques like PET and SPECT scans are crucial. They let doctors see how tumors are working on a cellular level, which is key for pinpointing the diagnosis and figuring out the best treatment. Combined PET-CT and SPECT-CT scans are especially helpful, offering deep insights into how tumors behave, how well treatment is working, and how the disease is changing over time[79]. Theragnostics is a rising star in child cancer care within nuclear medicine. It merges imaging for diagnosis with targeted radiation treatment, creating custom treatments that match the unique traits of each tumor. This method targets cancer cells precisely, sparing healthy tissue and making treatment more effective and safer[80]. Nuclear medicine imaging, especially 18F-FDG PET/CT scans, plays a vital role in understanding and treating brain tumors in children. These scans give doctors important details about how the tumor uses glucose, amino acids, and proteins. This information is crucial for distinguishing between different types of brain tumors, planning the right treatment, and checking how well the treatment is working[81]. In pediatric cardiology, nuclear medicine imaging is key to checking blood flow in the heart muscle, inflammation in the cardiovascular system, and how well the heart's nerves are working. It gives functional and predictive insights that add to what doctors can see with other imaging methods, providing a full picture of heart health in children with cancer[82].

5. MULTIDISCIPLINARY TREATMENT APPROACH TO PEDIATRIC ONCOLOGY

5.1 Surgery

In the field of pediatric surgery, treating childhood cancer patients involves innovative techniques and strategies. Minimally invasive surgery (MIS) has become increasingly important, offering advantages like reduced trauma, quicker recovery, and better cosmetic outcomes. Experts recommend strategic diagnostic and therapeutic surgical approaches for pediatric oncology[82]. Additionally, robotic-assisted laparoscopic techniques are showing promise in managing renal tumors in children, with encouraging initial results[83]. In pediatric oncology surgeries, preoperative planning has advanced significantly. Techniques like MRI-based 3D visualization help with procedures such as nephron-sparing surgery for Wilms' tumor[84]. Additionally, fluorescence-guided surgery has improved precision in techniques like sentinel lymph node biopsy[85]. Researchers are also exploring computer-assisted surgery systems that use artificial intelligence to enhance precision in pediatric oncological surgeries[86]. In pediatric neuro-oncology surgery, researchers have extensively studied intraoperative MRI-guided resection[87]. However, the evidence supporting a significantly better extent of resection with this technique remains inconclusive. Additionally, thoracoscopic surgery plays a crucial role in managing childhood cancer[88]. Video-assisted thoracoscopic surgery is also employed in pediatric oncology, but ongoing debates continue regarding its advantages compared to open surgery[89]. While there have been advancements in surgical approaches and technologies for pediatric oncology, challenges remain particularly in low- and middle-income countries where the burden of surgically treatable childhood cancers is substantial. It's essential for surgeons to follow sound principles of pediatric surgical oncology to achieve local control and enhance survival rates in young cancer patients[90].

5.2 Chemotherapy

Chemotherapy is a crucial part of treating pediatric cancer, effectively managing various childhood cancers. However, chemotherapy-induced nausea and vomiting (CINV) can significantly impact young patients undergoing treatment. To prevent CINV in pediatric patients receiving chemotherapy, guidelines recommend using dexamethasone in combination with other antiemetics[91]. Recent updates have also included palonosetron as part of the prophylactic regimen, highlighting the importance of optimizing antiemetic strategies in pediatric oncology. Apart from its effects on cancer cells, chemotherapy can also disrupt the intestinal microbiota, resulting in complications like chemotherapy-induced mucositis[92,93]. By understanding how the microbiota influences the severity of mucositis, we can develop strategies to minimize these adverse effects in pediatric patients undergoing chemotherapy. The occurrence of mucositis in children receiving chemotherapy underscores the importance of implementing supportive care measures to effectively manage treatment-related side effects[94,95]. In addition, the costs related to pediatric oncology treatment, including chemotherapy, can create financial difficulties and income poverty for families with children undergoing cancer therapy. It's crucial to address these socioeconomic challenges to ensure that pediatric oncology patients and their families have fair access to comprehensive care[96]. Amid the COVID-19 pandemic, there have been delays in starting chemotherapy for newly diagnosed pediatric cancer patients. These delays pose challenges in managing the disease and could impact treatment outcomes. Ensuring timely initiation of chemotherapy is essential to prevent disease progression and enhance treatment effectiveness in young cancer patients.

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Ensuring that healthcare providers adhere to chemotherapy guidelines is essential for achieving the best outcomes in pediatric oncology[97]. Quality improvement initiatives that address chemotherapy administration, handling, infection control, and patient safety play a crucial role in enhancing the overall care provided to young cancer patients[98]. Implementing strategies to improve guideline-concordant care for preventing chemotherapy-induced nausea and vomiting (CINV) in children undergoing chemotherapy is vital for enhancing treatment experiences and outcomes.

5.3 Radiation Therapy

Radiation therapy (RT) is a vital part of the comprehensive treatment for pediatric cancer. Approximately 50% of cancer patients, including children, receive RT[99]. It is commonly used to treat various pediatric cancers, including CNS tumors, solid tumors, Hodgkin lymphoma, and brain tumors[100,101]. RT plays a significant role in managing pediatric malignancies, and its effectiveness is well-established in the field of pediatric oncology. Radiation therapy is a key part of treating brain tumors in children, playing a crucial role in their overall treatment plan. Recent advancements in this technology, especially with proton beam therapy, show promise in minimizing damage to healthy tissues surrounding the tumor. This is particularly important for children, as they are more sensitive to radiation's harmful effects and have a higher risk of developing other cancers later on due to radiation exposure[102]. Proton therapy is often preferred over traditional photon therapy for these reasons, aiming to reduce both immediate and long-term side effects[103]. Providing radiation therapy to children with cancer requires special attention and facilities, particularly for urgent care needs. These young patients often receive treatment at centers primarily designed for adults, which means they need specific resources and emergency plans tailored to them104. On top of that, the Society for Palliative Radiation Oncology (SPRO) is committed to improving palliative radiation therapy. They focus on research, education, teamwork, and advocating for patients to ensure they receive the best possible care at the end of life[105]. To make sure radiation therapy is both safe and effective for children, it's crucial that pediatric radiation oncologists receive thorough training. There are suggestions to improve this training to ensure children with cancer get the best care possible[11,106]. Additionally, to overcome the challenges in places where there aren't enough resources, there are creative solutions being implemented, like online training programs, to build more expertise in pediatric radiation oncology[107].

5.4 Target Therapy

Targeted therapy is showing great promise in treating children with cancer by offering treatments that are more focused and effective. This approach has been made possible by progress in understanding the genetic makeup of tumors and finding specific targets to attack within them. Doctors can now look at the genetic details of a child's cancer to create tailored treatment plans. These plans often include targeted therapies, which are being tested in clinical trials and used in regular treatment, making care for young cancer patients more personalized and successful[108]. Precision medicine has made great strides in treating childhood cancers, with the FDA giving the green light to many targeted drugs specifically for these young patients. These drugs are designed to hit cancer right at its genetic weak points, which means they can be both more effective and less harmful than traditional treatments[109]. Moreover, cutting-edge genetic testing techniques are now being used in pediatric cancer care to find genetic changes that can be directly targeted by these new therapies, moving beyond old-school treatment methods[110]. In the world of childhood cancer treatment, early-stage clinical trials are now often testing targeted therapies, showing a shift towards more personalized medicine[111]. These trials are proving that such therapies can work for children and tend to cause fewer serious side effects than older, more general cancer treatments[112]. The success of these trials underlines the value of precision medicine in treating young cancer patients, focusing on finding and attacking specific targets within the cancer cells to improve the chances of successful treatment[113]. Targeted therapy is becoming a beacon of hope for treating brain tumors in children, especially with new medicines that are designed to get past the blood-brain barrier a major hurdle in treating brain conditions. These specialized treatments are being developed to effectively reach and treat brain tumors in young patients[114]. Additionally, the use of targeted therapies that act on specific parts of cancer cells is broadening the horizons for treating pediatric cancers, opening up possibilities for better treatment results and improved quality of life for these children[115].

5.5 Immunotherapy

Immunotherapy is a cutting-edge and hopeful strategy in the fight against childhood cancers, providing new paths to treatments that are more focused and effective. Research has been illuminating both the promise that immunotherapy holds and the hurdles it faces in the field of pediatric oncology. A major breakthrough in immunotherapy for children's cancer care is the use of specialized antibodies, like anti-GD2 therapy, for treating kids with high-risk neuroblastoma. Research, including studies by Yu and others, has shown that this type of immunotherapy, combined with GM-CSF and interleukin-2, leads to better results than traditional treatments[116]. The success seen with anti-GD2 therapy highlights the potential of immunotherapy to increase survival rates for children facing high-risk neuroblastoma[117]. Yet, bringing immunotherapy into childhood cancer treatment is not without its hurdles. There have been cases of side effects from immunotherapy in children, which highlights how crucial it is to watch for and manage these issues carefully[118]. Moreover, the distinct immune characteristics of cancers in children add complexity but also offer chances to develop new and innovative treatment approaches in pediatric oncology[119]. Testing in labs has shown that using immunotherapy together with radiation therapy could be a powerful combination for treating children's brain tumors and sarcomas. Nowadays, many clinical trials for children are exploring this combination as part of their standard treatment plans, suggesting that these two methods might work better together. This teamwork between cancer-fighting drugs and radiation could lead to better treatment results[119]. In particular, immunotherapy is making strides in

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treating brain tumors in children, showing remarkable results in those who haven't responded well to usual treatments. One exciting development is CAR T-cell therapy, which is designed to attack specific targets on pediatric solid tumors and has shown promise in early studies, pointing to a future where treatments are tailored to each child's cancer[120]. Even though there are obstacles and complexities in using immunotherapy for childhood cancers, researchers and clinical trials are actively investigating how this approach can lead to better results for young cancer patients. The exciting progress in immunotherapy offers hope for more effective and precise treatments, which could significantly improve both the outlook and the quality of life for kids undergoing cancer treatment.

5.6 Stem Cell Transplant

Stem cell transplant is a key part of treating childhood cancers, offering a chance to cure various blood cancers and solid tumors in kids. A lot of research has been done on how to best manage stem cell transplants, what results to expect, and what challenges might come up in treating young cancer patients this way. A crucial part of stem cell transplant care in children with cancer is handling common issues like fever and low white blood cell counts. Experts have set up rules for dealing with these problems quickly and effectively to prevent infections and improve the chances of a good outcome, as noted by Lehrnbecher and colleagues[121]. Also, there's ongoing research into using antifungal drugs, such as isavuconazole, to protect children with blood diseases and those receiving stem cell transplants from fungal infections[122]. Tools like the Pediatric Invasive Fungal Risk Score have been created to spot children with cancer or those who've had stem cell transplants who are at a high risk for serious fungal diseases. This helps catch these infections early and start treatment sooner to protect these at-risk kids[123]. Also, having a set way to test for infections, such as Clostridioides difficile, in children's cancer and stem cell transplant units has been key to making sure diagnoses are accurate and improving how well patients do[124]. Researchers have been looking into how stem cell transplants can affect children with acute lymphoblastic leukemia (ALL) who also have certain genetic changes, such as rearrangements in the MLL gene. They've been studying how effective stem cell transplants are for babies with ALL who are in their first remission and have these MLL gene changes, highlighting how important this treatment can be for certain groups of young cancer patients[125]. There's been a lot of focus on how to handle infections, such as those caused by Clostridium difficile, in kids with cancer and those who've received stem cell transplants. Experts have come up with guidelines to prevent and treat these infections in young cancer patients and stem cell transplant recipients, stressing the need for good infection control practices in these vulnerable children[126]. The different therapeutic methods used for the treatment of pediatric oncology are shown in Figure 3.

6. CHALLENGES AND FUTURE DIRECTIONS

The battle against childhood cancer is a testament to the power of modern medicine. We've seen remarkable strides in transforming once-fatal diseases into treatable conditions. This success stems from decades of refining chemotherapy and other treatments, leading to higher survival rates and reduced side effects[127]. Our growing knowledge about the long-term impacts of these treatments has been crucial in shaping gentler therapies and creating comprehensive care plans for survivors. These plans are now setting the standard for adult cancer care as well[127].

However, our work isn't done. As we continue to tweak therapies, it's vital to monitor their long-term consequences on new generations of young cancer patients. For instance, the shift towards using dexamethasone in treating Acute Lymphoblastic Leukemia (ALL) has led to an uptick in osteonecrosis cases. This has sparked important research into identifying who's at risk and how it affects their lives down the line. By keeping a close eye on these developments, we can ensure that our victories over cancer don't come with a steep price for those we're trying to heal. In addition, it's crucial to keep an eye on the long-term outcomes of reducing anthracycline doses. We need to understand if this approach truly lowers the risk of cardiomyopathy or merely postpones the emergence of heart issues[128]. It's equally important to implement proven strategies that lessen the aftereffects of cancer and its treatment on life quality, health complications, and survival rates. We should also be innovating and evaluating new methods.

Take, for instance, survivors of Hodgkin's Lymphoma who underwent chest radiation; they face a heightened risk of lung cancer later in life, a risk that skyrockets with tobacco use[129]. By promoting anti-smoking measures among these individuals, we can significantly cut down the likelihood of this serious adult cancer, while also curbing heart disease and other cancers linked to smoking. Early screening for breast cancer is already recommended for young women who had chest radiation. Moreover, childhood cancer survivors, especially those treated with radiation affecting the brain's hormone control center, are prone to obesity a condition that can worsen heart disease risks tied to anthracycline and chest radiation[130]. Addressing these interconnected health concerns is vital for safeguarding the long-term well-being of survivors.

Cardiovascular risk factors, like high blood pressure, can amplify the chances of serious heart conditions in cancer survivors. Both lifestyle changes and medical treatments have the potential to lower these risks[131]. We need research to pinpoint the best strategies for intervention and to develop comprehensive care models for survivors. While we've seen a rise in five-year survival rates for blood cancers like leukemias and lymphomas over recent years, progress for many solid tumors has hit a standstill. To reignite momentum, we must invest in research that uncovers new, groundbreaking treatments. These should be based on our deepening understanding of the cellular mechanisms that fuel tumor growth. Achieving this goal will likely span from fundamental research to practical applications, with a focus on translating lab discoveries into clinical trials. These trials should target specific biological characteristics of patient groups, fostering even stronger collaboration among childhood cancer research communities worldwide[132]. Addressing changeable heart health risks, such as high blood

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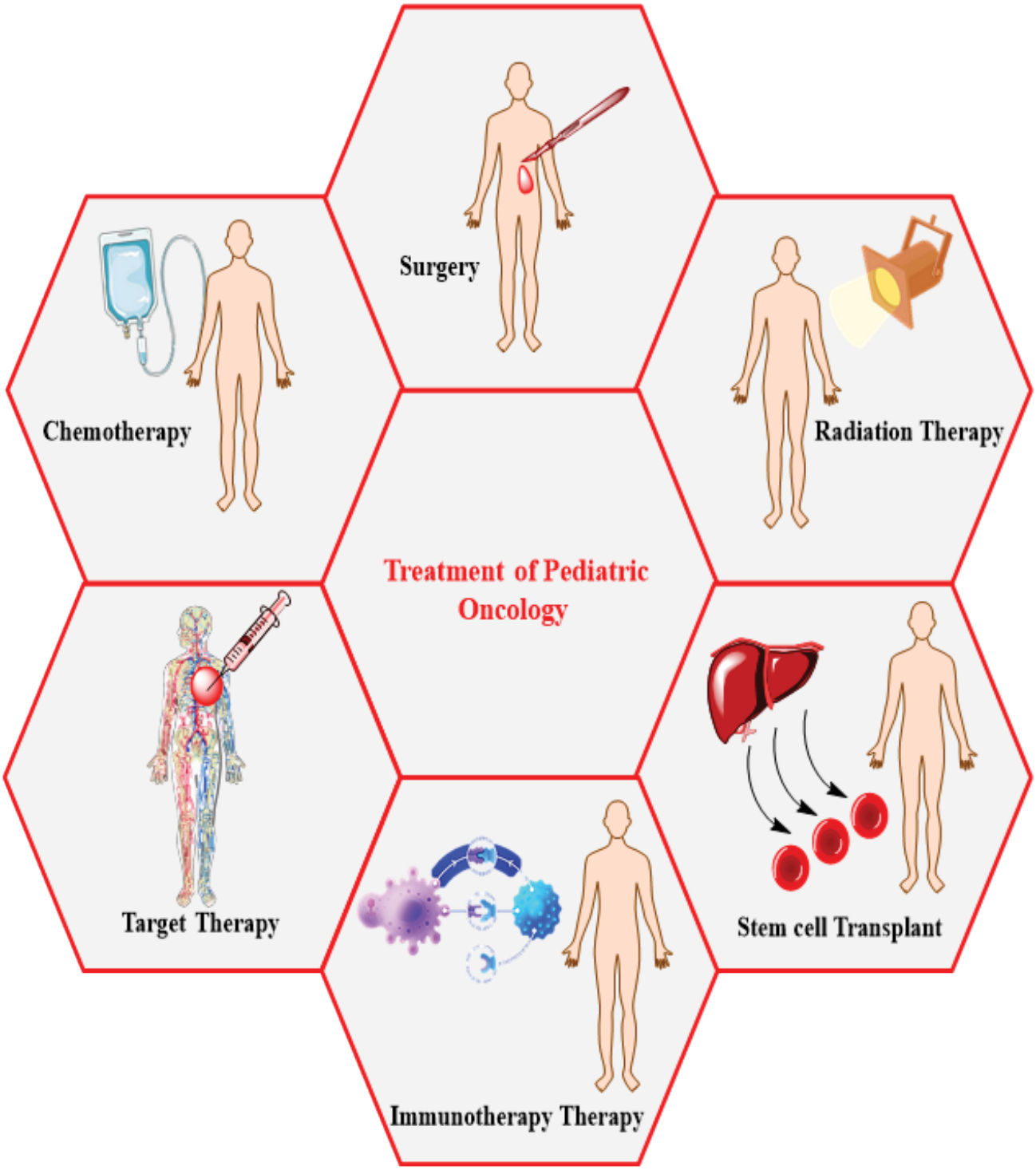

Figure 3. Different methods for the treatment of pediatric oncology.

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pressure, is key in preventing major heart problems for cancer survivors. Both lifestyle adjustments and medical treatments can help reduce these risks. It's essential to conduct research to find the most effective intervention methods and to create well-rounded care plans for survivors. In the past decade, we've seen an encouraging increase in the five-year survival rates for cancers like leukemias and lymphomas. However, for many solid tumors, there hasn't been much improvement in survival rates for the last 10 to 20 years. To push forward, we must focus on research that leads to new and inventive treatments. These should leverage our growing knowledge of how cancer cells grow and survive[133]. This research will span from basic science to practical application, requiring a translation of laboratory findings into clinical trials that focus on specific groups of patients based on their biological characteristics. This approach will need even more collaboration among national and international groups dedicated to childhood cancer clinical trials[134].

CONCLUSION

In conclusion, pediatric oncology is at a critical juncture, facing increasing cancer rates among children worldwide. This review underscores the necessity for improved healthcare access, affordable treatments, and equitable care to address the disparities in survival outcomes. By leveraging advancements in diagnostic technologies and treatment modalities, there is potential to significantly enhance the prognosis and quality of life for young cancer patients. The article calls for a concerted global effort to overcome socioeconomic barriers and to invest in personalized medicine and collaborative research. Such initiatives are paramount to driving progress in pediatric oncology, ultimately aiming to provide every child with the best chance at a healthy future.

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