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Review

DICER1 Tumor Syndrome: A Retrospective Review and Future Perspectives

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Abstract: DICER1 syndrome, a rare autosomal dominant genetic disorder, stems from mutations in the DICER1 gene, disrupting RNA interference and leading to various tumors. These tumors, affecting organs like the lung, kidney, ovaries, and brain, pose diagnostic challenges due to diverse presentations. Understanding DICER1-associated tumors, including pleuropulmonary blastoma, ovarian Sertoli–Leydig cell tumors, and others, is vital for early detection and management. Surgical resection, chemotherapy, and targeted therapies are primary treatment modalities, with genetic counseling playing a crucial role. Multidisciplinary care is essential for optimal management, offering hope for improved outcomes in affected individuals.

Keywords: DICER1; pleuropulmonary blastoma; genes; children; pediatric pathology

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1. Introduction

DICER1 syndrome (OMIM 606241, 601200) (or DICER1-pleuropulmonary blastoma familial tumor predisposition syndrome) is a rare autosomal dominant genetic disorder caused by mutations in the DICER1 gene, located on chromosome 14q32.13, and characterized by incomplete/reduced penetrance [1,2]. This syndrome was first identified in 2009 and has since garnered increasing attention in the medical community due to its complex array of associated manifestations [2,3]. The DICER1 gene encodes an enzyme (with a molecular weight of 200 kDa) called Dicer, which plays a crucial role in the process known as RNA interference, a physiological mechanism within cells that regulates gene expression by controlling the production of specific proteins called micro-RNAs (miRNAs). When the DICER1 gene is mutated, it can lead to the dysregulation of this process, resulting in various neoplastic and non-neoplastic diseases [1]. One of the hallmark features of DICER1 syndrome is the development of multiple benign and malignant tumors, often at a young age [3], affecting various organs, including the lung, kidney, ovaries, brain, thyroid gland, and others. Some of the most common tumors associated with DICER1 syndrome include pleuropulmonary blastoma, cystic nephroma, Wilms' tumor, anaplastic kidney sarcoma, ovarian Sertoli–Leydig cell tumors, embryonic rhabdomyosarcoma, and, more rarely, brain tumors such as pineoblastoma, nasal chondromesenchymal hamartoma, and medulloepithelioma of the ciliary body [4,5]. In addition to tumors, DICER1 syndrome may also be associated with a range of other clinical manifestations, such as thyroid abnormalities (multinodular goiter, MNG), eye abnormalities, and certain developmental disorders [4]. The severity and specific symptoms of DICER1 syndrome can vary widely among affected individuals, even within the same family [5]. Diagnosing DICER1 syndrome can be challenging due to its diverse presentation and the rarity of the condition;

however, advancements in genetic testing techniques have improved the ability to identify mutations in the DICER1 gene, aiding in diagnosis and management [6]. In this review article, we summarize the literature data regarding DICER1 syndrome, discuss the most important kind of tumors associated in this setting, and provide insights regarding the potential therapeutic principles applied to the treatment of this syndrome.

2. Materials and Methods

Literature research was conducted on PubMed, Web of Science, and Scopus until March 2024 using the following keywords: "DICER1 syndrome", "DICER1-pleuropulmonary blastoma familial tumor predisposition syndrome", "DICER1 gene", and "pediatric pathology". Duplicate publications were removed, two authors carried out the research separately, and the articles were discussed among all authors. On a few chosen papers, backward literature research was carried out.

3. Results

3.1. Epidemiology

DICER1 syndrome is considered a rare genetic disorder, with an estimated prevalence of fewer than 1 in 100,000 individuals [7] and 1:4600 in the oncological population. The true incidence and prevalence may vary across different populations and ethnic groups, and the prevalence of DICER1 syndrome may be underestimated due to underdiagnosis and underreporting, as well as variability in clinical presentation [3,7]; anyway, the available information comes from family-based studies, clinical case series, and retrospective analyses of tumor registries [5].

3.2. Etiology

DICER1 syndrome is primarily caused by germline mutations in the DICER1 gene, which is located on the long arm of chromosome 14 (14q32.13) [1] and encodes an endoribonuclease enzyme of the RNase III family called DICER1, which plays a crucial role in the process of microRNA (miRNA) synthesis [5]. miRNAs are short non-coding RNA molecules that regulate gene expression by binding to messenger RNAs (mRNAs) and either inhibiting their translation or promoting their degradation [8]. Specifically, most of the tumors are caused by a single germline DICER1 mutation, mostly a loss-of-function mutation (or also haploinsufficiency or dominant negative effects on DICER1 enzyme activity), and an acquired somatic missense DICER1 mutation near five hotspot codons in the RNase IIIb domain (E1705, D1709, G1809, D1810, and E1813) [5,7,9–11]. miRNA-mediated functions are fundamental for cells' response to oxidative stress, hypoxia, and DNA damage, and the resulting dysregulation of miRNA processing and function have widespread effects on gene expression (at the post-transcriptional level) and cellular pathways, contributing to the development of various benign and malignant tumors and other clinical features associated with DICER1 syndrome. In addition to germline mutations, somatic mutations in DICER1 can occur in specific cells, leading to the development of sporadic tumors associated with DICER1 syndrome. Somatic mutations may arise during embryonic development or throughout life and can contribute to tumor initiation and progression [7]. Furthermore, DICER1 syndrome exhibits genetic heterogeneity, with a wide range of mutations identified such as missense, nonsense, frameshift, splice-site mutations, and large genomic deletions or duplications. It is important to underscore that the location and type of mutation may influence the severity of clinical manifestations and the risk of specific tumor types. Finally, the clinical phenotype of DICER1 syndrome can vary widely among affected individuals, even within a family with the same underlying mutation, and this variability is attributed to factors such as genetic modifiers, environmental influences, and stochastic events; indeed, individuals may carry DICER1 mutations but remain asymptomatic or develop only mild clinical features, while others may experience severe or life-threatening complications [8,9].

Many of the clinical and pathological characteristics of subjects carrying the DICER1 mutation are related to the impairment of branching morphogenesis of the epithelium,

which is orchestrated and regulated by DICER1; in detail, all the organs that originate from this process (lung, kidney, liver) can be affected in various ways, with different levels of severity, depending on the extent of the impairment of the function of DICER1 [9–11].

3.3. Tumors DICER1-Associated

3.3.1. Pleuropulmonary Blastoma (PPB)

PPB was first described in 1988 [12], and it represents the most common primary pulmonary malignancy in children; although the exact cause of PPB remains unclear and no specific risk factors have been identified, there may be a genetic component in some cases, as PPB is associated with DICER1 syndrome [13]. Today, it is known that PPB presents four different histological forms (Type I, IR, II, and III), which constitute the spectrum of the disease. Type I PPB is characterized by cystic lesions of different size and number, lined by benign epithelial cells. These cysts may vary in distribution within the lung parenchyma and are often surrounded by a fibrous capsule. Histologically, the lining epithelium typically resembles fetal lung tissue, with cuboidal or columnar epithelial cells exhibiting uniform nuclei and minimal cytologic atypia. The stroma surrounding the cysts may contain immature mesenchymal elements, such as spindle cells and immature cartilage [14]. Previously considered as a form of congenital pulmonary airway malformation (CPAM) type IV, type I PPB must differentiate from type II PPB for the absence of a grossly detectable mass, and complete sampling is of paramount importance so as to not miss any features of the lesion [5]. The tumor cells may show rhabdomyoblastic differentiation, or they may require staining with desmin and myogenin using immunohistochemistry (IHC). The small cells are diffusely positive for CD56, which nonetheless makes them qualify as type I PPBs, even in the absence of a rhabdomyoblastic differentiation. Furthermore, a small percentage of otherwise architecturally comparable multicystic lesions without the primitive round cells is characteristic of type IR PPB, suggesting that the cystic PPB has either failed to complete tumor growth or may have suffered regression [15].

Type II PPB represents an intermediate stage in the spectrum of PPB, featuring a combination of cystic and solid components [16]. The cysts in type II PPB are lined by both benign and malignant cells, exhibiting varying degrees of cytologic atypia, nuclear pleomorphism, and mitotic activity. The solid areas consist of primitive blastema-like cells with scant cytoplasm and a high nuclear-to-cytoplasmic (N/C) ratio, resembling embryonal or undifferentiated sarcoma [5]. In some cases, type II PPB may also contain areas of rhabdomyoblastic differentiation, characterized by the presence of strap or strap-like cells with eosinophilic cytoplasm and cross-striations [16].

Type III PPB represents the most aggressive form of the disease, consisting predominantly of solid, undifferentiated sarcomatous elements with minimal or absent cystic components. Histologically, type III PPB exhibits high-grade nuclear features, brisk mitotic activity, and frequent areas of necrosis. The tumor cells may display primitive mesenchymal differentiation, including features suggestive of embryonal rhabdomyosarcoma, undifferentiated pleomorphic sarcoma, or other high-grade sarcomas [5,16,17].

In terms of overall survival (OS), both type I and type IR have earlier onsets, but both have good prognoses—98% and 100% of patients, respectively, survive for five years. In one study, it was found that older children are more likely to be diagnosed with type II and type III PPB, which had 5-year OS estimates of 75% and 53%, respectively [18].

3.3.2. Cystic Nephroma (CN) and Anaplastic Kidney Sarcoma (AKS)

CN is a rare benign renal tumor characterized by cysts of varying sizes within the kidney, accounting for less than 1% of all renal tumors [19]. It typically occurs in children under the age of 5, with a slight female predominance, and usually, it is unilateral [20]. Some cases may be associated with genetic syndromes like Beckwith–Wiedemann syndrome or tuberous sclerosis complex, both in DICER1 and non-DICER1 settings [21]. Histologically, CN is characterized by cysts lined by flattened or cuboidal epithelium surrounded by fibrous stroma. The cysts may contain clear or serous fluid, and the solid components

may contain spindle cells, stromal cells, or immature renal tissue. Having understood the pathogenesis of DICER1-associated neoplasms, it is interesting to understand whether the biological progression described in cases of type I PPB to type II/III PPB can also be applied to cases of pediatric CN. From the analysis of the studies available in the literature, it would seem plausible to argue that there are rare cases of CN transforming into anaplastic kidney sarcoma (AKS), supported by morphological and immunohistochemical characteristics, as well as by different pieces of reported evidence [22,23]. It is therefore mandatory to ensure a program for the screening of the pediatric population in question, not only for PPB but also for CN [5].

3.3.3. Wilms Tumor (WT)

In the setting of DICER1 syndrome, the occurrence of WT (or nephroblastoma), known best for being present in the setting of mutations/deletions in WT1 (11p13), has also been described. In detail, when WT occurs in a DICER1 carrier, the age of onset tends to be earlier than in sporadic cases, with a peak in infancy and early childhood; furthermore, these cases tend to be bilateral and/or multifocal, either simultaneously or sequentially. From a morphological point of view, some differences compared to sporadic WT have been described, including a greater probability of cystic changes, the occasional presence of heterologous elements, and unusual growth patterns [24,25]. Recently, some authors reported a case of a 3-year-old female with two synchronous lesions of PPB in the left lower pulmonary lobe and WT in the right kidney, underlining the possibility of two lesions in the setting of DICER1 syndrome [26].

Figure 1A–C present two examples of WT in the setting of DICER1 syndrome.

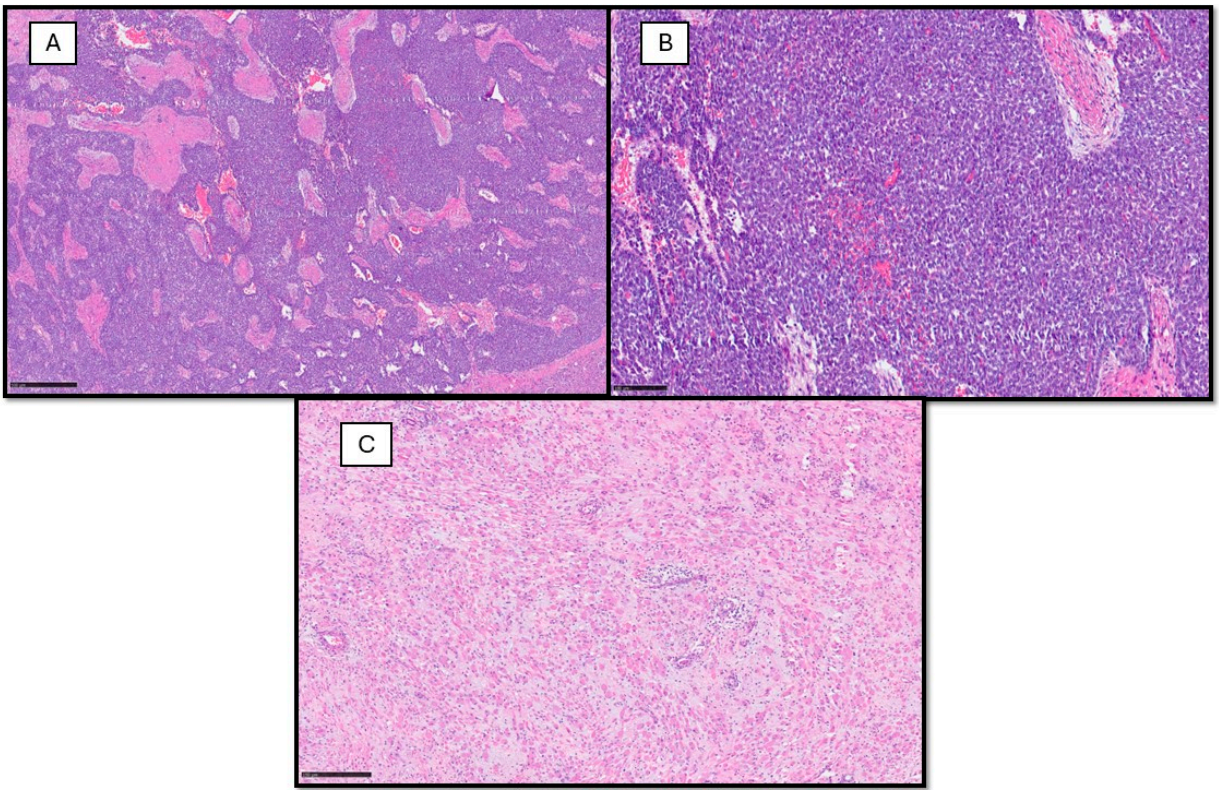

Figure 1. (**A**) Histological photomicrograph showing a mixed nephroblastic tumor (Hematoxylin–Eosin, original magnification 4×). (**B**) Scanning magnification of a field of the previous picture showing the tightly packed blue cells (blastema component) of this case of DICER1-related Wilms Tumor (Hematoxylin–Eosin, original magnification 20×). (**C**) Histological preparation showing heterologous differentiation of rhabdomyoblastic type in the same case (Hematoxylin–Eosin, original magnification 10×).

3.3.4. Ovarian Sertoli–Leydig Cell Tumors (OSLCTs)

OSLCTs are the most common ovarian tumors in DICER1 syndrome, but there are other types, such as germ cell tumors, juvenile granulosa cell tumors, yolk sac tumors, teratomas, and mixed germ cell tumors [27]. From a histological point of view, SLCTs, in the context of DICER1 mutations, are often moderately to poorly differentiated and may exhibit heterologous elements such as cartilage nodules and rhabdomyosarcoma, similar to other DICER1-associated tumors [28], while well-differentiated SLCTs have less of an association with DICER1 mutation, with only around 12% of cases reported in one study [29]. Heravi-Moussavi et al. conducted the first comprehensive analysis of DICER1 mutations in Ovarian Sex Cord–Stromal Tumors (OSCSTs), identifying mutations in 60% of SLCTs, predominantly located in the RNase IIIb domain of DICER1, and a subset of cases also had a second germline mutation in addition to the somatic mutation [30]. Other studies have reported a similar incidence of DICER1 mutation in SLCTs, ranging from 32% to 98% of cases, with the variability in mutation rates being partially attributed to enriched population bias for DICER1 carriers in some studies [28,31,32]. Given that DICER1-associated SLCTs typically present at a younger age than sporadic SLCTs, appropriate tissue testing is recommended due to the strong association of DICER1 mutation in SLCTs, particularly in younger patients with moderately to poorly differentiated SLCTs with specific histological features.

3.3.5. Embryonal Rhabdomyosarcoma of the Cervix (cERMS)

In DICER1 carriers, cERMS affects older children, adolescents, and young adults, with a median age of presentation around 13–14 years, contrasting with vaginal RMS, which typically presents at a median age of 2 years [33]. It is important to underscore that a biopsy of an ERMS from the vagina does not differentiate between vaginal and cervical origins, but additional clinical factors and studies may aid in distinguishing between the two [5,33]. Usually, cERMS exhibits the features of favorable botryoid ERMS, often characterized by a cambium layer, and approximately 50% of cases show foci of cartilage, a unique feature within the DICER1 setting (like PPB), unlike sporadic ERMS, where cartilage is usually absent [34]. An association between cERMS and SLCTs has been reported in several cases, suggesting a potential link beyond chance association, and some patients with cERMS have a prior history of SLCT, and vice versa, indicating a possible shared underlying genetic predisposition [35,36].

3.3.6. Gastrointestinal Tumors

Two cases of hepatic lesions described as “mesenchymal hamartoma” of the liver (MHL) were reported in young boys, aged 26 months and 75 months, and both cases were found to have heterozygous pathogenic DICER1 variants, with accompanying somatic mutations, including a hot-spot RNase IIIb DICER1 mutation in one case and a heterozygous in-frame germline deletion in the other [37]. However, dispute arose regarding the classification of these cystic hepatic tumors as MHL due to their molecular characteristics and histological features; indeed, MHL is characterized by a loosely cellular myxoid stroma with scattered, dysplastic bile ducts and isolated islands of hepatocytes, but the DICER1-associated hepatic lesions did not fit the classic MHL morphology, leading to suggestions that they represent another type of cystic liver lesion [38]. In any case, Gonzàlez et al. [5] described a case of a multicystic hepatic lesion in a 1-year-old child with a DICER1 germline mutation. The cysts were epithelial-lined and surrounded by a concentric fibrous stroma and a layer of rhabdomyoblasts in the cambium, which resembled the histological and architectural characteristics of type I PPB. With a DICER1 mutation, this new cystic hepatic tumor was identified from conventional MHL and its pathogenetic relationship to liver undifferentiated embryonal sarcoma.

3.3.7. Other Tumors

Although detailed pathology features of intestinal polyps in the context of DICER1 syndrome are not extensively reported, they appear to align more with hamartomatous-

types. Cases of children with DICER1 mutations presenting with multiple small intestinal polyps, bowel obstruction, and other associated tumors such as PPB and CN have been reported. These polyps have been described as "juvenile polyps" and "hamartomatous polyps," lacking specific histologic descriptions in some cases [39]. As reported [5], there were two recent additions to the spectrum of DICER1-associated tumors: pleuropulmonary blastoma-like peritoneal sarcoma and presacral malignant teratoid neoplasm. The first is similar to PPB but occurs in the peritoneum, and reported cases include seven children aged 3 to 14 years, with the primary sites identified as the fallopian tubes, pelvic sidewall, and serosa of the colon; none of these children had a past or contemporaneous history of PPB or other DICER1-associated neoplasms. From a histological perspective, these tumors have characteristics that are similar to PPB, such as cystic spaces with primitive small cells underneath, either with or without rhabdomyoblastic differentiation. The range of morphologies that are seen includes nodules of cartilage resembling type I PPB, multilocular peritoneal cysts that resemble type IR PPB, and solid multipatterned primitive sarcomas that resemble type II/III PPB [40]. Pancaldi et al. [41] first reported a case of a 16-year-old female with a history of MNG presenting with a widely metastatic abdominal small round blue cell tumor exhibiting neuroectodermal differentiation, termed PNET with EWSR1 rearrangement.

As reported in the last World Health Organization (WHO) Classification of Pediatric Tumours [42], thyroid nodules are very common in individuals carrying a germline pathogenic loss-of-function variants, and more than 50% of female DICER1 variant carriers develop multinodular goiter in their lifetime [43–45]. Indeed, in this syndrome, multinodular goiter can develop at a young age and may be associated with a higher risk of thyroid cancer. Furthermore, individuals have an elevated risk of developing certain types of thyroid cancer, particularly the follicular variant of papillary thyroid carcinoma (FVPTC) and poorly differentiated thyroid carcinoma (PDTC) [46–49].

Finally, DICER1 syndrome may also be associated with other thyroid abnormalities, such as ectopic thyroid tissue or thyroid hemiagenesis (underdevelopment of one lobe of the thyroid gland), and it also may be associated with an increased risk of developing non-thyroidal tumors such as parathyroid adenomas or salivary gland tumors [50]. Interestingly, Niedziela et al. [51] reported a case of a 4-year-old boy with a germline DICER1 pathogenic variant (c.2062C > T, p.R688*) and five relatives, as well as a somatic DICER1 mutation (c.5438A > G, p.E1813G) in the PPB DNA, that presented a hypoechogenic lesion with pseudomicrocalcifications in the right lobe of the thyroid, resulting in thymic ectopic tissue. This work underscores the importance of careful work-ups in the presence of these kinds of abnormalities.

Nasal chondromesenchymal hamartoma (NCMH) is characterized by the proliferation of disorganized cartilage and mesenchymal tissue within the nasal cavity and paranasal sinuses and typically presents as a painless nasal mass or obstruction, often in young children. NCMH has been recognized as a characteristic tumor associated with DICER1 syndrome, and histologically, NCMH exhibits a mixture of mature and immature cartilage, fibrous tissue, and myxoid stroma, without evidence of malignancy [52,53].

Finally, it is important to mention the potential presence of central nervous system (CNS) tumors during DICER1 syndrome, including pituitary blastoma [54,55], pineoblastoma [56], primary DICER1-associated central nervous system sarcoma [57,58], and embryonal tumor with multilayered rosettes (ETMR)-like cerebellar tumor [59,60]. Regarding the primary intracranial sarcoma DICER1-mutant, in a recent paper [57], the utility of H3K27me3 and TLE1 immunostains was demonstrated in the six cases analyzed.

Recently, Erber et al. reported a case of 65-year-old woman with a painless mass in her left buccal mucosa near the parotid duct, with no prior neoplasm history. Histopathological evaluation showed a fibroepithelial lesion resembling a phyllodes tumor within the dilated salivary duct, with goblet cells, ciliated epithelium, and sebaceous elements. Immunohistochemistry revealed varied marker expression, indicating stromal and epithelial components. Molecular analysis identified a DICER1 mutation (p.[Pro1645fs]), always

affecting the RNase IIIb domain, likely leading to loss of function. The authors defined this lesion as botryoid fibroepithelial polyps [61].

Regarding non-neoplastic conditions, a group [62] demonstrated that GLOW syndrome, comprising global developmental delays, lung cysts, somatic overgrowth, macrocephaly, and Wilms tumors, is related to the activation of the PI3K/AKT/mTOR pathway, influenced by the disruption of miRNA regulation due to DICER1 mutations.

Table 1 summarizes the different kinds of tumors in DICER1 settings.

Table 1. DICER1-associated tumors divided by organs.

Lung	Kidney	SNC Head and Neck	Gastrointestinal Endocrine	Gynecological Soft Tissue
Pleuropulmonary blastoma (PPB) I, IR, II, III	Cystic nephroma	SNC sarcoma with PPB III-like features	Cystic hepatic neoplasm with type I PPB-like features	Sertoli–Leydig cell tumor with/without heterologous differentiation and type I PPB-like features
PPB-like neoplasms	Anaplastic sarcoma of the kidney	Ciliary body medulloepithelioma	Hamartomatous polyp with juvenile polyp-like features	Peritoneal, ovarian, and fallopian tube sarcoma with PPB-like features
PPB-like Sertoli–Leydig cell tumor of lung		Pituitary blastoma	Cervical–thyroid teratoma	Cervical embryonal rhabdomyosarcoma
		Pineoblastoma	Malignant teratoid neoplasm of sacrococcygeal region	
		Embryonal tumor with multilayered rosettes	Multinodular goiter	
		Nasal chondromes-enchymal hamartoma	Papillary thyroid carcinoma	
		Botryoid fibroepithelial polyps of parotid duct	Follicular carcinoma	
			Poorly differentiated thyroid carcinoma	

4. Genetic Counseling

Genetic counseling is of paradigmatic importance in the correct recognition of DICER1 syndrome, with particular attention being paid to the screening programs that need to be implemented in this patient population [56,57,60–65]. In particular, a Danish cohort study has explored this aspect in depth by studying young cases (under 25 years) of thyroidectomy for MNG and found a particularly high incidence of DICER1 syndrome, allowing for the extension of strong recommendations for screening for this syndrome in subjects with MNG at a young age [66]. Furthermore, in a recent paper [66], the authors tried to determine the incidence of neoplasms in DICER1 carriers, enrolling patients from the International PPB/DICER1 Registry, the NCI Natural History of DICER1 Syndrome study, and the International Ovarian and Testicular Stromal Tumor Registry. All participants had either a history of DICER1-associated tumors or carried a pathogenic germline DICER1 variant. The study ultimately included 207 participants, predominantly non-Hispanic white, and interestingly, among nonprobands diagnosed with neoplasms, significant familial patterns were observed, with parents and offspring showing higher neoplasm counts compared to siblings and grandparents.

Elevated risks for known DICER1-associated neoplasms were noted, with additional findings including rare cancers not previously linked to DICER1. The study found no significant excess risk for some common adult cancers (melanoma, prostate cancer, and breast cancer). These data are sufficient for surveillance recommendations, including chest CT scans and periodic pelvic ultrasounds for the early detection of PPB and gynecologic

tumors. Finally, thyroid evaluations every three years unless nodules are detected, followed by age-appropriate guidelines for further evaluation, were recommended.

A paper by Apellaniz et al. [63] presented a case of a male infant diagnosed with a low-grade paratesticular myxoid tumor with strong WT1 and CD10 expression and also a cystic nephroma, underscoring the possibility of this tumor being of Mullerian origin in the context of the pathogenic germline DICER1 variant and different somatic hotspot mutations.

5. Therapeutic Approaches

Therapeutic approaches in DICER1 syndrome vary depending on the specific tumor types and associated conditions. Surgical resection is often the primary treatment modality for DICER1-associated tumors, aiming at achieving complete excision while preserving surrounding healthy tissues. The extent of surgical intervention depends on factors such as tumor size, location, and histological characteristics, and the surgical techniques may include endoscopic or open approaches, depending on the tumor's location and complexity [67]. Chemotherapy may be used as an adjuvant or neoadjuvant therapy in the treatment of DICER1-associated tumors, particularly for those with a high risk of recurrence or metastasis. Chemotherapeutic agents commonly used in the management of DICER1-related malignancies include platinum-based drugs, taxanes, and anthracyclines, and the specific chemotherapy regimen and duration of treatment depend on the tumor type, stage, and individual patient factors [68]. Radiotherapy may be employed as part of the treatment approach for certain individuals with aggressive or recurrent disease [69]. Targeted therapies that specifically target molecular pathways implicated in tumor growth and progression may hold promise for the treatment of DICER1-associated malignancies. In detail, molecularly targeted agents such as tyrosine kinase inhibitors, mTOR inhibitors, and PARP inhibitors are being investigated in preclinical and clinical studies for their potential efficacy in DICER1-related tumors, and these targeted therapies may offer new treatment options for patients with refractory or recurrent disease, particularly those with tumors that harbor specific molecular alterations [70].

Genetic counseling and screening play a crucial role in the management of DICER1 syndrome, as identifying individuals with germline DICER1 mutations allows for early detection and the surveillance of associated tumors. Family members of individuals with DICER1 mutations should undergo genetic counseling and testing to assess their risk of developing DICER1-associated tumors and to implement appropriate surveillance measures [71–73].

6. Concluding Remarks

DICER1 syndrome is a rare genetic disorder characterized by germline mutations in the DICER1 gene, leading to an increased risk of developing a wide range of benign and malignant tumors across multiple organs. This article highlights the diverse spectrum of DICER1-associated tumors, including pleuropulmonary blastoma, ovarian Sertoli–Leydig cell tumors, nasal chondromesenchymal hamartomas, and others. Understanding the clinical manifestations, histopathological features, and molecular mechanisms underlying DICER1 syndrome is crucial for early detection, accurate diagnosis, and the optimal management of affected individuals. Multidisciplinary care involving collaboration among oncologists, surgeons, geneticists, and other specialists is essential for providing comprehensive treatment and genetic counseling to patients and their families. Further analyses of the molecular pathways involved in DICER1-associated tumorigenesis and the development of targeted therapies hold promise for improving outcomes and quality of life for individuals with this rare genetic disorder.

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