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Type I and Ir Pleuropulmonary blastoma (PPB): A Report from the International PPB/*DICER1* Registry

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Abstract

Background: Pleuropulmonary blastoma (PPB) is the most common lung cancer of infancy and early childhood. Type I PPB is a purely cystic lesion with a microscopic population of primitive small cells with or without rhabdomyoblastic features which may progress to type II or III PPB, whereas type Ir lacks primitive small cells.

Methods: Children with suspected PPB were enrolled in the PPB/*DICER1* Registry. Pathology was centrally reviewed, and follow-up was ascertained annually.

Results: Between 2006 and 2022, 205 children had centrally reviewed type I or Ir PPB; 39% of children with type I and 5% of children with type Ir PPB received chemotherapy. Outcomes were favorable, although 11 children (9 with type I and 2 with type Ir) experienced progression to type II/III (n=8) or regrowth of type I PPB at the surgical site (n=3), none of whom received chemotherapy prior to progression. Age and cyst size in combination were more suitable than either factor alone in predicting whether a particular lesion was type I or Ir PPB.

Conclusion: For young children with type I PPB, outcomes are favorable, but complete resection is indicated due to risk for progression. Chemotherapy may be useful in a subset of children at increased risk for recurrence/progression. Efforts to risk stratify children with type I PPB to optimize outcomes while reducing treatment-related side effects are underway.

Precis:

Outcomes for children with type I and Ir PPB are favorable, although progression to advanced PPB is noted in some children. Chemotherapy may be useful in a subset of children with type I PPB at increased risk for recurrence/progression.

Keywords

Pleuropulmonary blastoma; Type I; Type Ir; *DICER1* ; *DICER1* syndrome

Introduction

Pleuropulmonary blastoma (PPB), the most common primary lung neoplasm of childhood, is unique among virtually all malignancies with its age-associated clinical and pathologic progression from a relatively innocuous-appearing multicystic lesion to a high-grade multipatterned sarcoma. Type I PPB, which includes a microscopic population of small primitive tumor cells with or without rhabdomyoblastic differentiation, may evolve into a mass composed of a complex sarcomatous collage with or without residual cystic foci designated as type II or type III PPB, respectively. Although progression from type I to type II or III is well described, type Ir (regressed) PPB, which is microscopically devoid of any subepithelial septal primitive cells, is thought to have a lower risk for malignant progression.[1,2]

Treatment for type I PPB has varied over time, with some children undergoing surgery alone and others undergoing surgery and adjuvant chemotherapy. Given its rarity and heterogeneity of clinical factors the optimal therapeutic regimen remains unclear. Following resection of a cystic lesion and a thorough pathologic evaluation, most type Ir PPBs have been followed clinically due to the reduced risk of tumor progression. Children with type I PPB who undergo complete resection are generally managed with surgery alone. However, chemotherapy has been given to some children with type I PPB following incomplete resection or for an unresectable cyst(s).[3]

In addition to their relevance as distinct clinical entities, type I and Ir (like type II and III PPBs) are associated with *DICER1* pathogenic variants, either in individuals with germline predisposition or in association with biallelic somatic mutations.[4] Germline pathogenic variants in *DICER1* are also associated with other conditions including but not limited to neoplasms of the kidneys, ovaries, peritoneum, brain, and thyroid.[5–15]

In this analysis, we describe clinical factors and outcomes in children with type I and Ir PPB. Additionally, given the clinical challenge of distinguishing type I from type Ir preoperatively, we compare clinical and radiographic features in histologically-proven type I and Ir PPB and present a potential predictive model.

Methods

Children with suspected PPB were enrolled in the International PPB/*DICER1* Registry. Informed consent and assent (when applicable) were obtained. All study procedures were approved by the relevant human subjects committees. Pathology was centrally reviewed by a Registry pathologist (LPD/DAH). This analysis included children with type I or Ir PPB centrally reviewed from May 2006—when central pathology review began distinguishing between type I and Ir—to April 2022. Individuals with a prior diagnosis of type II/III PPB were excluded. Treatment remained at the discretion of the treating physician/institution.

Information from medical records was systematically ascertained including demographic, clinical, surgical and pathologic variables, treatment and time-to-event outcomes. Cyst size was summarized using the volume of an ellipsoid (0.5236*length*width*height) when all three dimensions were measured; maximal dimension of the largest cyst was used for cysts

with at least one dimension reported. Genetic and molecular data were obtained using previously described techniques[16] or abstracted from clinical records. Operative reports were centrally reviewed and abstracted (DM). Extent of resection was subcategorized as gross total resection with negative margins (R0), gross total resection with positive margins (R1), macroscopic residual (R2) or subtotal resection. Cases with known presence of more than one cystic lesion were classified as multifocal disease. Cystectomy and wedge resection were combined and distinguished from lobectomy. For patients with multiple surgeries, best degree of resection was reported. Time-to-event (from diagnosis) outcomes included overall survival (OS) and PPB-event-free survival (EFS); the latter events were defined as recurrence of type I at the surgical site or progression to type II/III PPB.

Associations with PPB type were assessed with chi-square (or Fisher exact test when necessary) and Mann-Whitney tests for categorical and numeric data, respectively. PPB-EFS and OS were estimated via Kaplan-Meier curves. Due to the small number of events, associations with clinical characteristics were assessed for EFS only among type I patients. Associations with potential prognostic factors were described with hazard ratios (HRs) from Cox proportional hazards regression, but confidence intervals were not reported due to small effective sample sizes; instead, associations were tested via Monte Carlo permutation test using the log-rank chi-square test statistic (with 10,000 replications). To compare patients with chemotherapy and surgery versus surgery alone, Kaplan-Meier curves were estimated for the two comparison groups, and an adjusted analysis used inverse probability of treatment weights to estimate survival curves and stratified log-rank test (using permutation distribution) after subclassifying patients on the propensity score.[17,18] For adjusted analysis, balance between covariate distributions was assessed using standardized differences, with absolute difference of <10% being considered well-balanced.[19] The propensity score model included age, sex, degree of resection, focality, spill/rupture, and maximum dimension of the cyst. Unadjusted survival curves by chemotherapy use were also reported stratified by prognostic risk factors, which were determined post hoc. A multi-variate model predicting type I versus Ir PPB was developed using generalized boosting models, a machine learning technique that allows a flexible functional form. Generalized boosted models with logit link function were used to estimate the probability that cysts were diagnosed as type I using the “gbm” library in R (R Foundation for Statistical Computing).[20] Using simple cut points based on the results of the boosted model, a post hoc logistic regression model was also used to describe this association.

Results

Of 597 cases of centrally reviewed PPB enrolled in the PPB/*DICER1* Registry, 244 had centrally-reviewed type I or Ir as their initial PPB diagnosis. Of these, 205 had initial diagnoses of type I (n=118) or Ir (n=87) PPB centrally reviewed between 2006 and 2022. The remaining 39 type I PPBs were excluded as they were centrally reviewed prior to the uniform distinction between types I and Ir PPB.

Type I PPB

Demographics/molecular/clinical results—Median age at diagnosis was 7 months (range 0.0–12.8 years); 95% were diagnosed prior to 3.1 years of age, with outliers at 7.9, 9.5 and 12.8 years (Table 1). Fifty-five percent were male. Six (5%) had a prior or concomitant history of cystic nephroma and one (1%) individual had a concomitant neuroblastoma. Most (68%) participants were from North America.

Germline *DICER1* results were available for 57 children; 75% had a germline *DICER1* pathogenic/likely pathogenic variant. Somatic testing showed biallelic mutations in 17 of 18 of tested tumors (94%).

Nearly all (96%) presented with a multiseptated lung cyst on imaging studies. Multifocal cysts were present in 27% of patients. The maximum cyst dimension ranged from 2 cm to 16 cm (median 7 cm). Most patients (82%) presented with clinical symptoms (32% with pneumothorax), 14% of cysts were found during evaluation for another condition, and 4% were found during routine surveillance. Pleural effusion was noted in 11% of patients. None presented with metastatic disease.

Operative/pathologic findings—Adhesions were noted intraoperatively in 33% (Table 2). A stalk or exophytic mass was noted in 24%. Cyst disruption or *in vivo* spillage was noted in 45%. No children had empyema or vascular invasion. Primitive small cells with or without rhabdomyoblastic differentiation were present in all cases with corroborating immunohistochemistry. Anaplasia was rarely noted. Local and central pathology results were discordant in 13% (Supplemental Table 1). Two patients were centrally reviewed as type I with early signs of transition to type II PPB. These patients were diagnosed at 18 and 25 months, were treated with combined vincristine, actinomycin-D and cyclophosphamide/vincristine and actinomycin-D and vincristine, actinomycin-D and cyclophosphamide, respectively, and remain in remission 47 and 21 months from diagnosis.

Surgery—Overall, 80% underwent a single surgery for a type I PPB; 17% underwent a second-look surgery and a small subset (3%) underwent a third procedure (Table 2). Cystectomy or wedge resection and lobectomy were performed equally. Extent of resection was R0 in 85%, R1 in 12%, R2 in 3%, and subtotal resection in 1%.

Chemotherapy—A single patient received neoadjuvant chemotherapy prior to surgery in addition to adjuvant chemotherapy (Table 2). Thirty-nine percent of patients received primary adjuvant chemotherapy.

Of the individuals who received chemotherapy, most (74%) received vincristine, actinomycin-D and cyclophosphamide (VAC). Two children received ifosfamide, vincristine, actinomycin-D and doxorubcin (IVADo), a regimen generally used for type II/III PPB; one of these had a treating institution diagnosis of type II PPB and completed treatment prior to central pathology review.

Outcomes—Follow-up data were available for 116 of 118 individuals. Nine children (8%) had recurrence/progression between 2 and 63 months after initial diagnosis and 5-year

PPB-EFS was 90.3% (95% CI 84.0–97.1) (Table 2, Fig. 1A). Specifically, three developed regrowth of type I at the site of resection and six had progression to type II/III PPB. Four of these lesions were initially diagnosed by the treating institution as congenital lung cysts and five as type I PPB. Six were centrally reviewed after the recurrence/progression. All 9 children with recurrence/progression underwent a single surgery at diagnosis; five R0, 2 R1 and 2 with no information on extent of resection. Of the 3 who experienced recurrence of type I, 2 underwent R1 resection. The third patient was 1 month of age at diagnosis and was found to have recurrent or potentially metachronous type I shortly after an R0 resection. Five of six patients with type I with progression to advanced PPB had multifocal cysts at diagnosis (2 with known residual cysts, 2 with no evidence of residual cysts and 1 with no information).

The 5-year OS was 98.0% (95% CI 94.3–100.0; Table 2, Fig. 1B). There was one late death 12 years after initial type I diagnosis in an adolescent with a history of progression to solid PPB and development of a central nervous system tumor 9 years after PPB treatment.

Table 3 reports associations of PPB-EFS with potential prognostic factors among the entire cohort and the surgery only cohort (i.e., no chemotherapy). R0 resection appeared protective relative to non-R0 resection, especially among patients who did not receive chemotherapy (HR=0.19, p=0.035). Patients with known multifocal cysts had worse outcomes than patients with no known multifocality among the entire cohort as well as within the surgery only group. Age at diagnosis, spillage, and cyst size were not associated with PPB-EFS.

Figure 2 displays comparisons of patients who received chemotherapy and surgery to those who underwent surgery only. No patients who received chemotherapy had an event, thus chemotherapy was protective with a 100% 5-year PPB-EFS rate versus 82.6% (95% CI 71.9–94.8) among the surgery only group (p=0.003). Notably, a greater portion of participants that received chemotherapy had known multifocal lung cysts and underwent less than R0 resection, but inverse probability of treatment and stratification on the propensity score led to improved balance on several factors (Supplemental Table 2, Supplemental Fig. 1). The propensity score analysis also suggests a protective association with chemotherapy with adjusted 5-year PPB-EFS rate of 82.4% (95% CI 71.8–94.5, Fig. 2B, p=0.034) among the surgery only cohort. When stratified by post hoc risk factor of extent of resection, the impact of chemotherapy appears greater among the higher risk non-R0 resection group (Fig. 2C–D). For example, among those who received only surgery, the patients who had less than R0 resection had lower 5-year PPB-EFS rate of 66.7% (95% CI 37.9–100.0) compared with 88.2% (95% CI 77.7–100.0) among the R0 resection group.

Additional conditions—In this cohort, 26 children developed 41 additional neoplasms, distinct from PPB progression, which were likely related to *DICER1* pathogenic variants (Supplemental Table 3, Fig. 1C). Twenty-two children had additional lung cysts; 7 with an additional surgery showing type Ir and fifteen with new lung cysts diagnosed by imaging but not resected. Thyroid nodules and additional neoplasms are summarized in Supplemental Table 4.

Type Ir PPB

Demographics/molecular/clinical results—The median age at diagnosis of type Ir PPB was 2.6 years (range 2 months-45 years) (Table 1). As in type I, most participants enrolled from North America (85%). Twelve children had a history of cystic nephroma, 4 with Sertoli-Leydig cell tumor (SLCT), 2 each with thyroid nodules and embryonal rhabdomyosarcoma of the uterine cervix. One patient each had a history of thyroid carcinoma, PPB-like peritoneal sarcoma[15], *DICER1*-associated hepatic cystic neoplasm[21], juvenile hamartomatous polyps, pineoblastoma, partially differentiated nephroblastoma (not centrally-reviewed) and ovarian sex cord-stromal tumor, not otherwise specified.

Results of germline *DICER1* testing was available for 60 patients and showed a pathogenic/likely pathogenic variant in 83%. Due to paucity of tumor cells, *DICER1* somatic testing is more challenging in type Ir; *DICER1* sequencing showed a somatic hotspot in 7 of 9 (78%) of successfully tested cases.

A multiseptated lesion was present in 74% of cases by imaging; 25% had multifocal cystic lesions. Maximum dimension ranged from 0.4 cm to 16 cm (median 4.2 cm). Fewer than half were symptomatic (38%), 25% were discovered incidentally during evaluation for another condition and 37% were found during surveillance for known *DICER1* variant, another *DICER1*-related condition or a positive family history. A small subset (12%) presented with pneumothorax.

Operative/pathologic findings—Adhesions were present in 21% at surgery (Table 2). A stalk or exophytic cyst was present in 23% of cases. Spillage or cyst disruption occurred in 19%. All showed a cystic lesion, architecturally identical to type I PPB but devoid of a primitive small cell population and/or rhabdomyoblasts localized beneath the epithelial lining of the cysts. Local and central pathology results were discordant in 55%, with 40% of discordant cases presenting with a treating institution diagnosis of type I PPB (Supplemental Table 1).

Surgery—Nearly all (93%) patients had a single surgery; the remainder underwent a second-look surgery (Table 2). Most were excised by cystectomy or wedge resection (63%). Extent of resection was R0 in nearly all (97%); one underwent R1 resection and one underwent subtotal resection.

Chemotherapy—Of individuals with type Ir PPB, 4 of 87 (5%) received chemotherapy based on local diagnosis prior to central review, residual cysts post-surgery or both (Table 2).

Outcomes—Follow-up data were available for 84 of 87 individuals. Five-year PPB-EFS was 96.4% (95% CI 91.6–100.0) (Table 2, Fig. 1A). Following the diagnosis of type Ir, two individuals progressed to type II/III PPB. Neither received primary adjuvant chemotherapy; progression to type II/III was detected at 7 and 21 months following their initial diagnosis. Both presented initially with unifocal cysts; one had R0 resection and the other had no information on extent of resection. Both were originally diagnosed as congenital lung cysts with tissue from initial diagnoses centrally reviewed after progression. Both progressions occurred at the site of original cyst resection. There were no PPB-related deaths in children

whose initial diagnosis was type Ir PPB (5- and 10-year OS 100%) (Table 2, Fig. 1B), however, one patient died of a meningeal sarcoma 15 years after original type Ir diagnosis.

Additional Conditions—In addition to type II/III PPB diagnoses listed above, 24 patients developed 32 additional neoplasms (Supplemental Table 3, Fig. 1D). Three had additional surgeries for metachronous type Ir PPB and 8 others had new lung cysts diagnosed by imaging but not resected. Thyroid nodules and additional neoplasms are summarized in Supplemental Table 4.

Surgical issues in type I and Ir PPB

In children with *DICER1*-related lung cysts, multiple cysts are common and cumulative number and extent of surgeries remains a clinical concern. Thus, in addition to analyses above, we also analyzed the number of total thoracic surgeries (Table 2). When considering thoracic surgeries overall, 76% of children had a single surgical event, 19% required two surgeries, 5% underwent three total surgeries and a single patient required a fourth surgery.

Predictive model for type I versus Ir PPB

Individuals with type Ir were older at diagnosis (median age 0.6 vs. 2.6 years, $p<0.001$); however, type Ir was diagnosed throughout the age spectrum in young children, adolescents and adults. After age 3, type Ir was considerably more common than type I PPB. Type I PPBs were also noted to have larger median maximal dimension and volume (Table 1, $p<0.001$). A larger cyst was more likely to be type I, however even cysts larger than 3 cm retained a substantial likelihood of type Ir and there was considerable overlap in size between diagnostic groups.

Figure 3 shows the probability of type I diagnosis as a function of age at diagnosis and largest cyst dimension using boosted regression model and a post hoc logistic regression model. A steep decline in probability of a type I PPB occurs around 2.5 years of age at diagnosis (Fig. 3A) and post hoc cut points were chosen at 1, 3, and 5 years at diagnosis. A similarly steep incline in probability of type I occurs for cyst sizes at or above 3 cm (Fig. 3B) and post hoc cut points were chosen at 2 and 4 cm. Figure 3C shows the combined boosted model of type I diagnosis as a function of age at diagnosis and largest cyst dimension. As an example, Fig. 3D provides predictive probabilities for specific ages and cyst sizes using the post hoc logistic regression model.

Discussion

In this analysis, we describe recent outcomes in children with type I and Ir PPB. There are significant differences ($p<0.05$) in the presentation and treatment of type I and Ir including age at diagnosis, prior history of a non-PPB tumor, septations visible by CT scan, symptomatic presentation, cyst volume and maximum dimension, pneumothorax, spillage/rupture, pleural effusion, number of surgeries, extent of resection, treatment with adjuvant chemotherapy and discordant local and central pathology results. Type I and Ir are generally associated with favorable outcomes, however progression to type II/III or regrowth of type I occurred in a small subset of children. More than half of the children with recurrence

or progression were initially diagnosed with a congenital lung cyst, likely resulting in less stringent decision-making regarding adequacy of surgery in comparison to an initial recognition of the lesion as a PPB.

We found chemotherapy to be protective with higher risk for recurrence/progression in children with type I undergoing surgery alone. In contrast, our previous analysis suggested chemotherapy had no effect on recurrence/progression in type I PPB.[1] Additionally, when considering patients with type I that underwent surgery alone, less than R0 resection and known multifocal disease were associated with a higher risk of recurrence/progression. Information on extent of resection was generally ascertainable by review of pathology and operative reports including central pathology and surgical review, whereas multifocality was less reliably obtained because post-operative imaging was often unavailable. We wish to highlight the clinical importance of post-operative imaging in confirming presence or absence of new or residual cysts, the latter potentially unmasked when a large adjacent cystic lesion is resected.

Despite being one of the largest cohorts of children with type I PPB, recurrence and progression are uncommon so effective sample sizes for survival analyses are quite small. Our statistical analysis addressed this issue using permutation analyses, but interpretation of results are difficult when there is little to no variation. In particular, although recurrence and progression appears to be rare for patients who received chemotherapy, we warn that the 100% PPB-EFS is an overestimate. While no recurrence/progression events were observed in children receiving chemotherapy in this cohort, an additional patient, diagnosed prior to this pre-defined time period, experienced progression following chemotherapy.

Progression was less likely after an initial diagnosis of type Ir PPB. Both type Ir progressions occurred within 2 years of diagnosis suggesting that the risk is low especially after 2 years. Time period of risk appears longer for type I where recurrence/progression was more frequent and occurred up to 63 months following surgery therefore we suggest that children with a history of type I PPB be monitored for at least 6 years following diagnosis.

In this analysis, we acknowledge the possibility of metachronous tumor development as an alternative to recurrence/progression, however, for the cases of progression reported here, previous surgical site was confirmed. *DICER1* hotspot testing on both samples was not generally available, however, currently if a child presents with suspected recurrence or progression of type I PPB, we recommend clinical tumor testing of both the original cystic PPB and the new tumor to distinguish true progression from metachronous tumor development via comparison of tumor specific “hotspot” variants in the RNase IIIb domain. Additionally, due to limited availability of tumor tissue and low number of progression events, ascertainment of molecular features associated with progression was not possible and should be the subject of future analyses.

This analysis represents the largest cohort to date of children with centrally reviewed types I and Ir PPB. Outcomes for children with type I PPB have improved over time. The previously reported 5-year OS for children with type I PPB was 89% in a cohort of 89 patients.[1] The cohort reported here was limited to cases centrally-reviewed after May 2006, based

on the time when the pathologic distinction was made between type I and Ir PPB. For type I PPB, we observed 5-year OS of 98.0% (95% CI 94.3–100.0); this improvement in survival may reflect advances in imaging or surgical techniques or increased preoperative awareness of a potential diagnosis of PPB, with alterations in surgical or clinical approach. The refinement in the pathologic distinction between type I and type Ir has reduced the potential for the incorporation of type Ir cases into the type I cohort with its effect on an increased OS. Thus, these results likely represent *bona fide* improvement from one or more aforementioned factors rather than differences based on histopathologic diagnosis. Notably, 4 patients with type I and 26 patients with type Ir were found due to routine surveillance for known *DICER1* pathogenic/likely pathogenic variants or family history followed by a surgical approach based on a preoperative presumptive diagnosis of PPB. Since the sentinel discovery of the linkage between PPB and pathogenic *DICER1* variants in 2009[4], we have observed an increase in the percent of cases identified by surveillance and expect this to further increase based on wider application of genetic testing and imaging-based surveillance.[22]

The current analysis includes only cases with a central pathology reviewed diagnosis of type I or Ir PPB. We note a high rate of discordance between treating institution and central pathology interpretation and thus continue to encourage central pathology review for all cases of suspected PPB. Most participants enrolled from North America, however, we hope that the information provided, especially with regard to central pathology review (offered at no charge) and emerging global collaborations will facilitate increased recognition of these rare tumors worldwide.

The risk of progression in unresected type I PPB is likely substantially higher than reported here and is not addressed by this analysis. Thus, despite the low rate of progression in these cases of resected type I and Ir, identification of type I to allow resection prior to progression to type II/III remains a high clinical priority. Unresected type Ir is likely a lower risk lesion due to lack of a primitive small cell population, but whether unresected type Ir may progress to type II/III in young children remains unclear. Since the pathologic distinction between type I and Ir is a central factor in management and potential outcome, a thorough and complete examination of the multicystic lesion with resection margins, if possible, is incumbent in all cases. An incomplete pathologic evaluation may result in an incorrect interpretation of type Ir with a diminished concern for recurrence or progression to type II/III PPB, although this diagnosis still merits caution and attention to clinical features. In type I, the subepithelial population of primitive small cells and/or rhabdomyoblasts may vary from widespread distribution throughout the lesion to more limited and patchy. These primitive small cells may lack the immunophenotype of rhabdomyoblasts with desmin and myogenic positivity but are CD56 positive. It remains equally important to distinguish a cystic PPB from congenital pulmonary airway malformation.

An important finding from this cohort is that although most individuals fare well, additional neoplasms such as SLCT and other *DICER1*-associated neoplasms were seen during follow-up, highlighting the importance of genetic testing (including cascade testing of first-degree and extended family members) and ongoing surveillance.[22,23] This must be considered logistically in the follow-up of these individuals, ensuring that they are either monitored in

the longer term by their pediatric oncology center (not always done in children who undergo surgery alone) or by a cancer predisposition clinic. This also highlights the importance of education for families, primary care providers, surgeons and other multidisciplinary health care providers.

Germline and tumor sequencing results were available for only a subset of the enrolled participants. Nonetheless, we wish to highlight the clinical importance of genetic testing for individuals with all forms of PPB. Testing and surveillance guidelines are now available to facilitate diagnosis of PPB in its earliest form, associated with a favorable prognosis as described here.[10,23] Detection of a pathogenic germline *DICER1* variant or mosaicism may also facilitate diagnosis of other *DICER1*-related conditions, some of which (e.g. SLCT) are known to be associated with a more favorable prognosis when detected at an early stage.[24,25]

Subsequent thoracic surgeries were performed in 25% of children with cystic PPB, raising the question of operative risks and potential long-term effects on lung function. A single case of post-operative stenosis of the ipsilateral pulmonary artery in a child presenting with a large type I PPB was observed. Although surgical intervention poses risks, early intervention may mitigate impact on pulmonary function as alveolarization continues during childhood.[26] A quarter of patients in this cohort had multifocal cysts, presenting a unique challenge as in some cases, not all cysts may not be safely removed. A systematic analysis of health-related quality of life in children with PPB is ongoing (www.PPBregistry.org).[27]

Based on the incidence of surgery in children with cystic PPB and the simultaneous need to prevent progression to type II/III PPB, we sought to identify clinical and radiographic factors to distinguish between type I and Ir PPB and to develop a predictive tool for this purpose. Although we feel this is a helpful tool meriting prospective evaluation with the ultimate goal of reducing surgeries over time, we have noted some limitations. First, in order to increase available sample size, we used cyst sizes from either imaging or pathology reports and used date of diagnosis as the date of surgery, not initial detection date, as this was more reliably ascertained. Moreover, the model only included confirmed cases of type I or Ir PPB and did not include other possible pathologic diagnoses (e.g., CPAM).

This analysis suggests increased risk for recurrence of type I PPB associated with less than R0 as best resection thus re-resection or chemotherapy should be considered for children with less than R0 with initial surgery. This analysis also found an increased risk associated with known multifocality however we caution that multifocality was incompletely assessed in this retrospective analysis. Currently, management of multifocality requires an individualized approach and ultimately, a prospective trial is encouraged to define the optimal management of individuals with cystic PPB. After resection, post-operative cross-sectional imaging may allow assessment for additional cystic lesions as well as surveillance for recurrence.

Conclusion

We have analyzed the largest-ever cohort of children with type I or Ir PPB. All children underwent surgery with central pathology review between 2006 and 2022; some underwent

more than one surgery to achieve gross total resection and/or resection of additional cystic lesions. Approximately 40% of children with type I PPB received chemotherapy. Outcomes were favorable and have improved over time, likely related to increasing recognition of type I PPB as a malignant entity, improved imaging techniques, careful surgical approach and judicious use of chemotherapy in a subset of individuals. The challenge remains to decrease the use of chemotherapy and associated toxicities while maintaining improved outcomes. Recognition of type I and Ir PPBs as distinct entities with recommendations for genetic testing are highlighted. Risk stratification efforts to define optimal therapy for children with type I PPB are ongoing and should be studied in the context of a prospective trial; international collaboration is encouraged.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflicts of interest:

Dr. Stewart provides telegenetics services for Genome Medical, Inc, in accordance with relevant National Cancer Institute policies. Dr. Hill is owner of ResourcePath LLC, a company which does research and development of laboratory tests including for DICER1 cancers. That work is unrelated to the information presented in this article. Dr. Kamihara has the following financial disclosures all via her spouse: Owner/founder: Rome Therapeutics; PanTher Therapeutics; TellBio, Inc.; Consultant: Tekla Capital; Ikena Oncology; Rome Therapeutics Research funding: ACD-Biotechne. The remaining authors have no conflicts to disclose.

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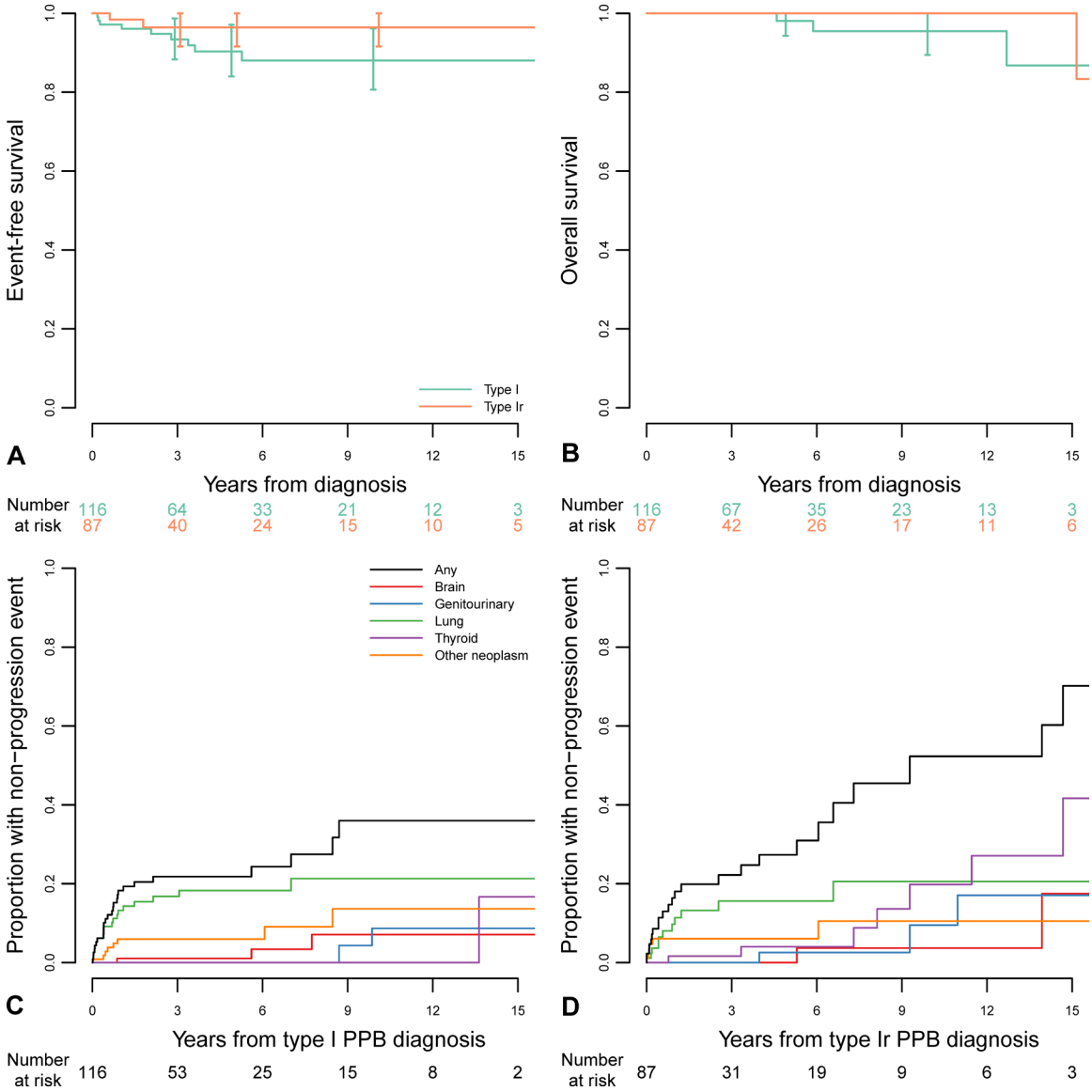


Figure 1.

PPB-event-free survival (**A**) and overall survival (**B**) in types I (green) and Ir (orange) PPB and proportion with subsequent non-progression event (e.g. a separate, typically *DICER1*-related condition) in children with type I (**C**) and type Ir (**D**) PPB. PPB indicates pleuropulmonary blastoma.

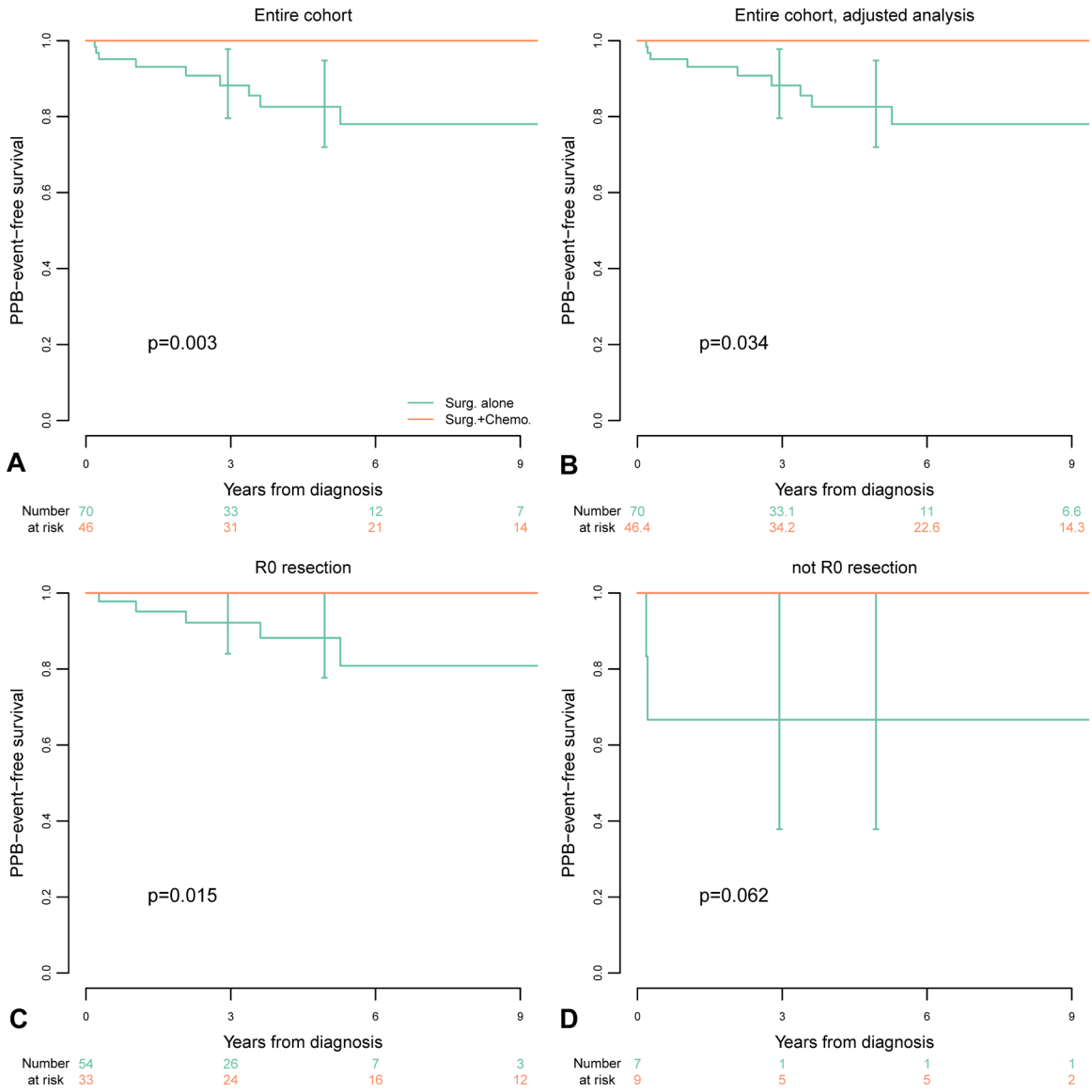
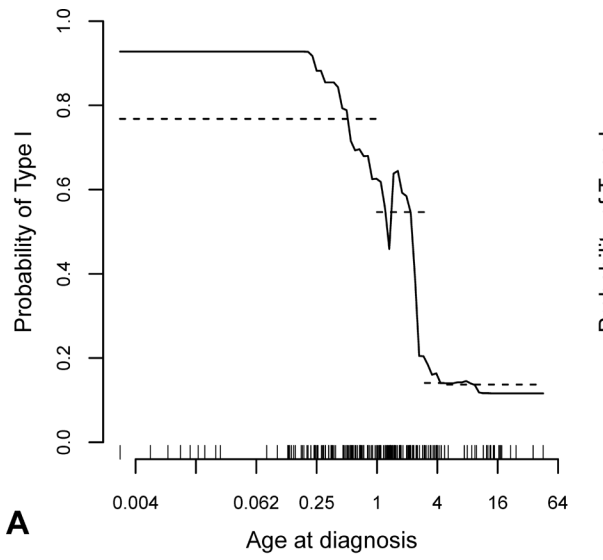
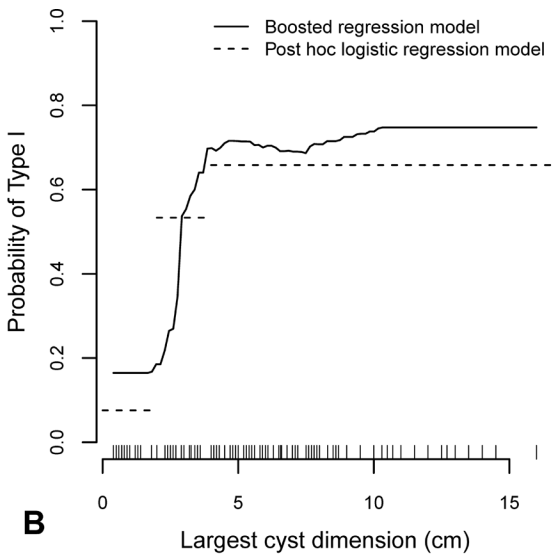
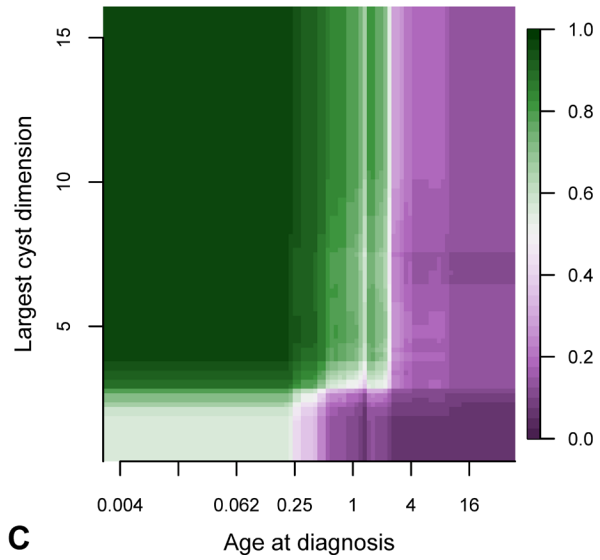


Figure 2.

Among type I pleuropulmonary blastoma (PPB) patients, PPB-event-free survival curves of patients who received chemotherapy and surgery (orange) versus surgery alone (green). Curves in (**A**) are unadjusted whereas curves in (**B**) are adjusted via inverse probability of treatment weighting with permutation p-value based on subclassification on the propensity score. The bottom two panels stratify on degree of resection; specifically, (**C**) includes patients with gross total resection with negative margins (R0) and (**D**) included patients with less than R0 resection.







Largest cyst dimension (cm)	Age at diagnosis (years)	N (%)	Probability of Type I, % (95% CI)
0 - 2	> 5	3 (2)	1 (0, 8)
0 - 2	3 -5	4 (2)	0 (0, 6)
0 - 2	1-3	11 (7)	4 (0, 25)
0 - 2	≤ 1	4 (2)	13 (2, 56)
2 - 4	> 5	3 (2)	15 (4, 45)
2 - 4	3 -5	2 (1)	9 (2, 36)
2 - 4	1-3	12 (7)	47 (27, 69)
2 - 4	≤ 1	15 (9)	78 (58, 90)
> 4	> 5	9 (5)	28 (9, 59)
> 4	3 -5	10 (6)	18 (5, 50)
> 4	1-3	33 (20)	66 (50, 79)
> 4	≤ 1	63 (37)	89 (79, 94)

Probability of Type I

D

Figure 3.

Predicted probabilities of type I vs type Ir diagnosis from generalized boosted model and post hoc logistic regression model with age at diagnosis and largest cyst dimension (n=174). **A**. Shows the probability of type I PPB based on age in years. **B**. Shows probability of type I PPB based on largest cyst dimension (cm). **C**. Shows the model of type I PPB diagnosis as a function of age at diagnosis and largest cyst dimension from boosted regression model. **D.** The probabilities for specific ages and cyst sizes for post hoc logistic regression model are provided. PPB indicates pleuropulmonary blastoma.

Table 1.

Demographic, molecular and clinical data for individuals with type I and Ir PPB.

		PPB Type I (n=118)	PPB Type Ir (n=87)	p-value
Demographics				
Age at Diagnosis (y), median (range)		0.6 (0.0 – 12.8)	2.6 (0.2 – 45.4)	**<0.001**
Sex	**Female, n/N (%)**	53/118 (45)	33/87 (38)	0.317
	Male, n/N (%)	65/118 (55)	54/87 (62)	
Prior non-PPB tumor history, n/N (%)		7/118 (6)	24/87 (28)[a]	**<0.001**
Molecular				
Germline *DICER1* P/LP variant or mosaicism, n/N (%)		43/57 (75)	50/60 (83)	0.572
Somatic (tumor) *DICER1* variant, n/N (%)		17/18 (94)	7/9 (78)	0.078
Clinical				
Multiseptated (per radiology), n/N (%)		65/68 (96)	31/42 (74)	**0.001**
Multifocal, n/N (%)		31/117 (27)	22/87 (25)	0.846
Laterality	**Right, n/N (%)**	55/116 (47)	42/86 (49)	0.466
	Left, n/N (%)	42/116 (36)	35/86 (41)	
	Bilateral, n/N (%)	19/116 (16)	9/86 (11)	
Maximum Cyst Volume (cm^3), median (range) (n)		56.4 (1.2 – 864.5) (n=82)	18.8 (0.0 – 733.0) (n=55)	**<0.001**
Maximum Cyst Dimension (cm), median (range) (n)		7.0 (2.0 – 16.0) (n=101)	4.2 (0.4 – 16.0) (n=76)	**<0.001**
How Diagnosed	**Symptomatic, n/N (%)**	78/95 (82)	27/71 (38)	**<0.001**
	Routine Surveillance, n/N (%)	4/95 (4)	26/71 (37)	
	Work up for another condition, n/N (%)	13/95 (14)	18/71 (25)	
Symptoms at Diagnosis	**Breathing Issues, n/N (%)**	75/78 (96)	26/27 (96)	0.973
	Fever/Pneumonia, n/N (%)	15/78 (19)	8/27 (30)	0.260
	Abdominal Pain/Malaise/Weight Loss, n/N (%)	8/78 (10)	5/27 (19)	0.261
Pneumothorax, n/N (%)		33/102 (32)	9/73 (12)	**0.005**
Pleural effusion, n/N (%)		11/98 (11)	2/72 (3)	**0.041**

cm = centimeters, cm^3 = cubic centimeters, P/LP = pathogenic/likely pathogenic, PPB = pleuropulmonary blastoma, n = number, N = number assessed, y = year

[a] 24 patients with 27 prior neoplasms

Table 2.

Surgical, treatment and outcome data for type I and Ir PPB.

		PPB Type I (n=118)	PPB Type Ir (n=87)	p-value
Surgical				
Adhesions, n/N (%)		27/81 (33)	14/66 (21)	0.103
Exophytic/Stalk, n/N (%)		21/86 (24)	15/65 (23)	0.848
Spillage, n/N (%)		39/87 (45)	13/68 (19)	**0.001**
Empyema, n/N (%)		0/99 (0)	0/72 (0)	-
Vascular invasion, n/N (%)		0/102 (0)	0/74 (0)	-
Anaplasia, n/N (%)		1/117 (1)	0/87 (0)	1.000
Number of chest surgeries at diagnosis	**1, n/N (%)**	94/118 (80)	71/87 (93)	**0.018**
	2, n/N (%)	20/118 (17)	6/87 (7)	
	3, n/N (%)	4/118 (3)	0/87 (0)	
Type of surgery	**Cystectomy/Wedge/Segment, n/N (%)**	55/111 (50)	52/82 (63)	0.055
	Lobectomy n/N (%)	56/111 (50)	30/82 (37)	
Extent of resection	**R0, n/N (%)**	88/104 (85)	76/78 (97)	**0.006**
	R1, n/N (%)	12/104 (12)	1/78 (1)	
	R2, n/N (%)	3/104 (3)	0/78 (0)	
	STR, n/N (%)	1/104 (1)	1/78 (1)	
Number of chest surgeries overall	**1, n/N (%)**	79/118 (67)	76/87 (87)	**0.006**
	2, n/N (%)	29/118 (25)	10/87 (12)	
	3, n/N (%)	9/118 (8)	1/87 (1)	
	4, n/N (%)	1/118 (1)	0/87 (0)	
Treatment				
Neoadjuvant chemotherapy, n/N (%)		1/118 (1)	0/87 (0)	1.000
Adjuvant chemotherapy, n/N (%)		46/118 (39)	4/87 (5)	**<0.001**
Chemotherapy Regimen	**VAC, n/N (%)**	34/46 (74)	1/4 (25)	0.064
	VAC/VA, n/N (%)	4/46 (9)	2/4 (50)	
	VA, n/N (%)	1/46 (2)	1/4 (25)	
	IVADo, n/N (%)	2/46 (4)	0/4 (0)	
	Other, n/N (%)	3/46 (7)	0/4 (0)	
	No Information, n/N (%)	2/46 (4)	0/4 (0)	
Outcome				
PPB-EFS	**3-year EFS, % (95% CI)**	93.4 (88.3–98.7)	96.4 (91.6–100.0)	0.146
	5-year EFS, % (95% CI)	90.3 (84.0–97.1)	96.4 (91.6–100.0)	
	10-year EFS, % (95% CI)	88.0 (80.6–96.1)	96.4 (91.6–100.0)	
OS	**3-year OS, % (95% CI)**	100.0 (100.0–100.0)	100.0 (100.0–100.0)	0.328
	5-year OS, % (95% CI)	98.0 (94.3–100.0)	100.0 (100.0–100.0)	
	10-year OS, % (95% CI)	95.5 (89.4–100.0)	100.0 (100.0–100.0)	

CI = confidence interval, EFS = event-free survival, IVADo = ifosfamide, vincristine, actinomycin-D and doxorubicin, OS = overall survival, PPB = pleuropulmonary blastoma, n = number, N = number assessed, R0 = gross total with negative margins, R1 = gross total with positive margins, R2 = macroscopic residual, STR = subtotal resection, VA = vincristine and actinomycin-D, VAC = vincristine, actinomycin-D and cyclophosphamide, VAC/VA = vincristine, actinomycin-D and cyclophosphamide/vincristine and actinomycin-D

Table 3:

Association of PPB-event-free survival with prognostic factors among the entire type I PPB cohort (n=116) and the surgery-only cohort (n=70).

		Entire cohort			Surgery only		
Prognostic factor	**Group**	**N**	**Hazard ratio**	**Permutation P-value**	**No.**	**Hazard ratio**	**Permutation P-value**
Resection	R1, R2, STR	16	Ref.		7	Ref.	
	R0	87	0.40	0.288	54	0.19	0.035
Multifocal	No	85	Ref.		54	Ref.	
	Yes	31	3.28	0.068	16	3.14	0.067
Spill	No	48	Ref.		28	Ref.	
	Yes	38	0.70	0.711	21	0.88	0.949
Age	< 1.5 years	92	Ref.		57	Ref.	
	≥ 1.5 years	24	0.45	0.463	13	0.52	0.525
Cyst size	0–5 cm	27	Ref.		12	Ref.	
	5–10 cm	58	0.96	0.925	42	0.67	0.649
	≥ 10 cm	15	0.94	0.904	7	1.02	1.000

cm = centimeters, PPB = pleuropulmonary blastoma, N.= number, R0 = gross total resection with negative margins, R1 = gross total resection with positive margins, R2 = macroscopic residual, Ref. = reference group, STR = subtotal resection