European Reference Network
for rare or low prevalence complex diseases
Network Paediatric Cancer (ERN PaedCan)

16 February 2023

Maria Kourti & Arianna Tagarelli

PLEUROPULMONARY BLASTOMA

Moderation: Gianni Bisogno

Funded by the European Union's EU4Health Programme

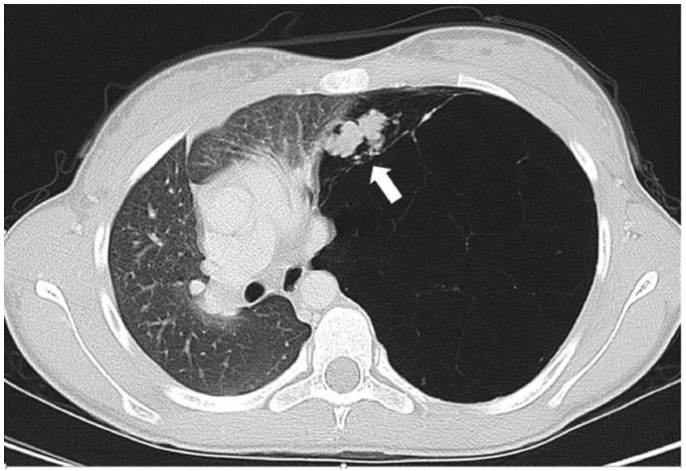
SIOP Europe
the European Society for Paediatric Oncology

St. Anna Kinderkrebs Forschung

COI declaration

Case presentation (1)

- 13-year-old female; Past Medical History : asthma
- Emergency Department : non-productive cough of one month duration and an abnormal chest radiograph showing left lung hyper-expansion with mediastinal shift, remodeling of the sternum, and no acute pneumonia.
- Physical examination : absence of breath sounds on the left
- Routine laboratory investigations: normal.



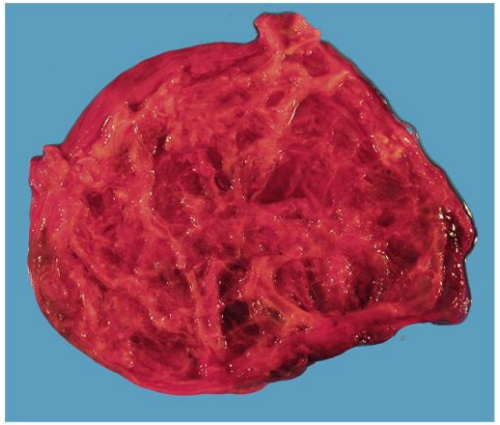
- Chest CT scan : a large, gas-filled, septated lesion occupying the majority of the left lung with pronounced rightward mediastinal shift.
  - The lesion demonstrated an internal nodular, lobulated solid focus which raised the concern for a potential underlying neoplasm, rather than a congenital pulmonary airway malformation (CPAM)

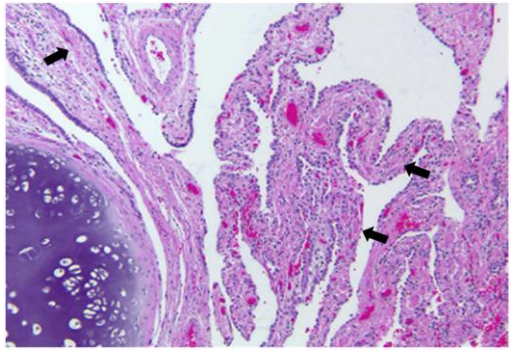
J Pediatr Surg Case Rep. 2020;59

Case presentation #1: treatment

- Video-assisted thoracoscopic resection of the left lower lobe lung lesion.
- Gross examination showed a 14.0 × 11.5 × 3.7 cm primarily cystic lesion with an irregular granular to nodular mass-like area.
- Histopathologic diagnosis was noted to be pleuropulmonary blastoma, type Ir.
- Negative for DICER 1

- No further treatment after surgery





J Pediatr Surg Case Rep. 2020;59

Case presentation #1: conclusion

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Pre adolescent female with PPB type Ir completly resected at diagnosis

What is the difference between PPB type I and PPB type Ir ?

How would you treat and follow up a type I and type Ir PPB?

What is the prognosis of type I and type Ir PPB?

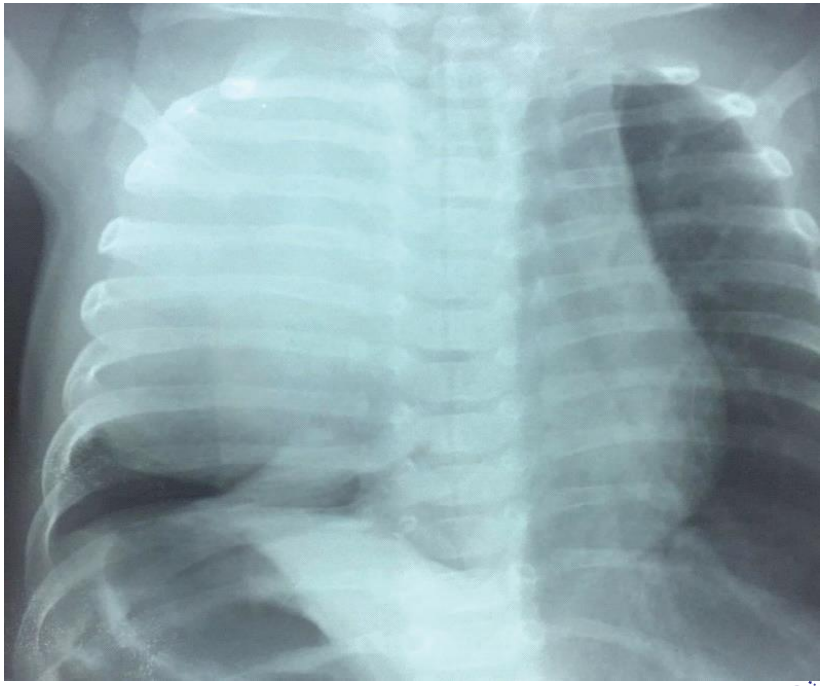
Case presentation (2)

- 4-month-old boy admitted to PICU
  - cough, dyspnea, cyanosis
  - afebrile
  - HR: 144bpm, SpO_2:86%
- No family history of genetic disease
- Normal lab tests

CASE REPORT | Med Arch. 2021;75: 61-65

Case presentation

- No breath sounds in the right pulmonary area
- Chest x-ray
- Ultrasonography
- CT scan



CASE REPORT | Med Arch. 2021; 75(1): 65

Case presentation

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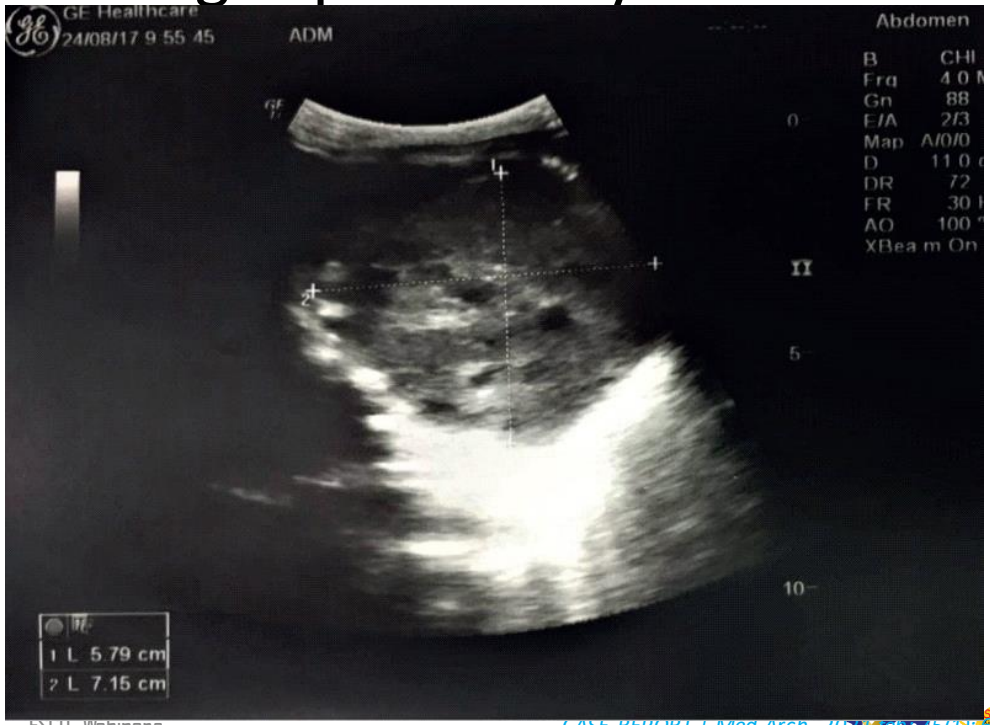

Case presentation

- No breath sounds in the right pulmonary area
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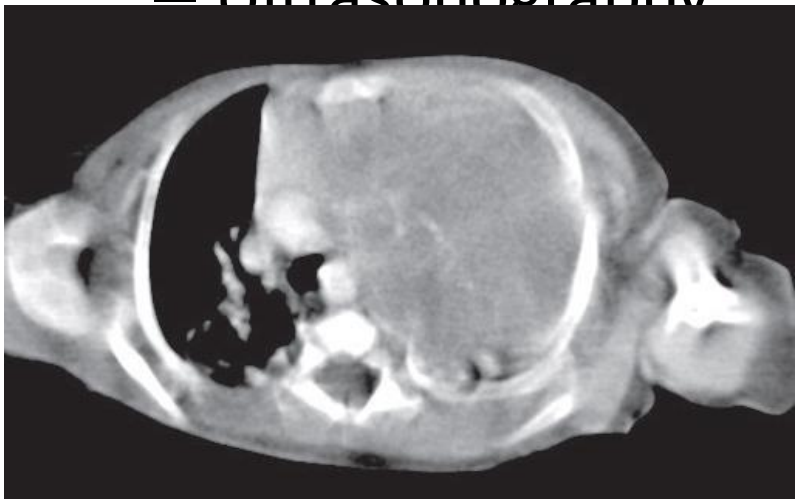
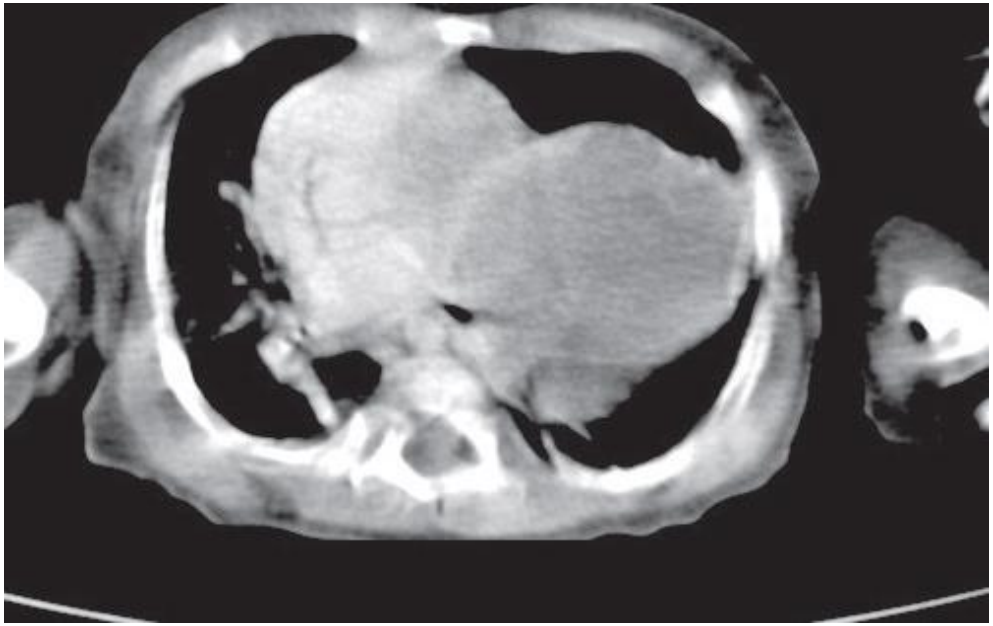




CASE REPORT | Med Arch. 2021; 75(1): 65

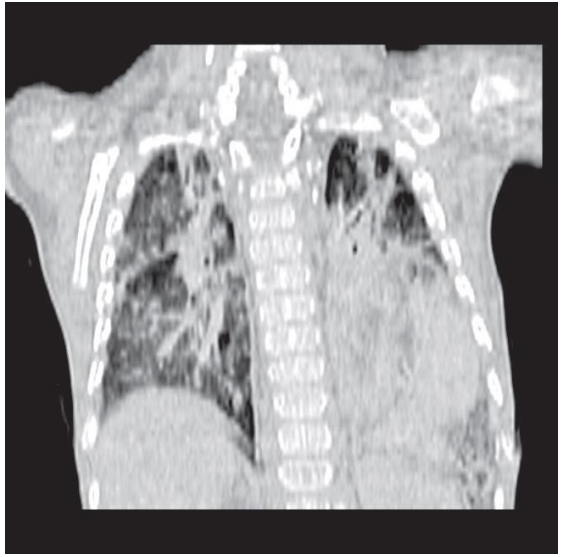
Therapy

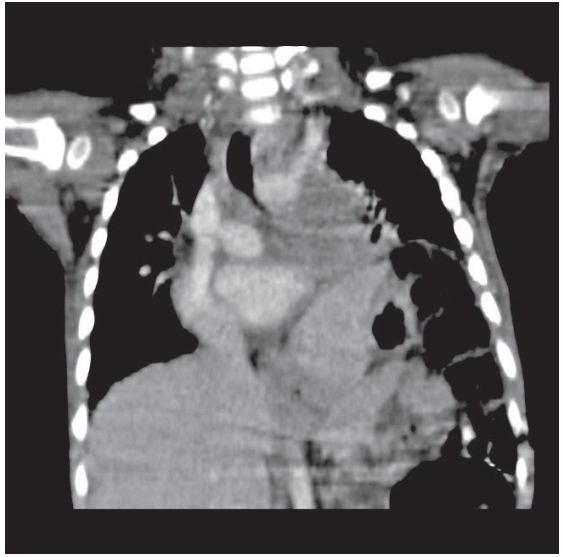
- Surgery (radical resection of a 7.0 x 5.0 cm mass that included cystic lesions.
- Histopathological examination confirmed the diagnosis of type II PPB
- Chemotherapy with the IVADo chemotherapy protocol (50% reductions in dosages, infant)
- Genetic analysis of germ line DICER1 mutations by NGS was negative.

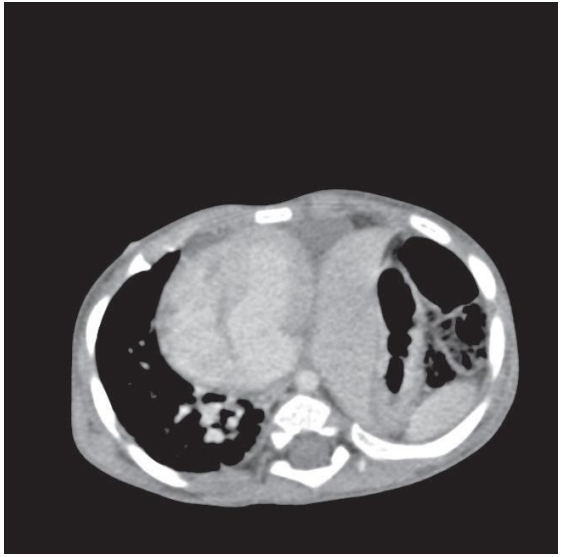
CASE REPORT | Med Arch. 2021;75: 61-65

Outcome

– A second CT scan performed 2 months after initiating chemotherapy treatment revealed a new, growing mass







Patient succumbed of respiratory distress followed by sepsis and cardiopulmonary arrest.

CASE REPORT | Med Arch. 2021;75: 61-65

Case presentation #2: conclusion

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– Infant with recurrent disease

How would you treat this patient?

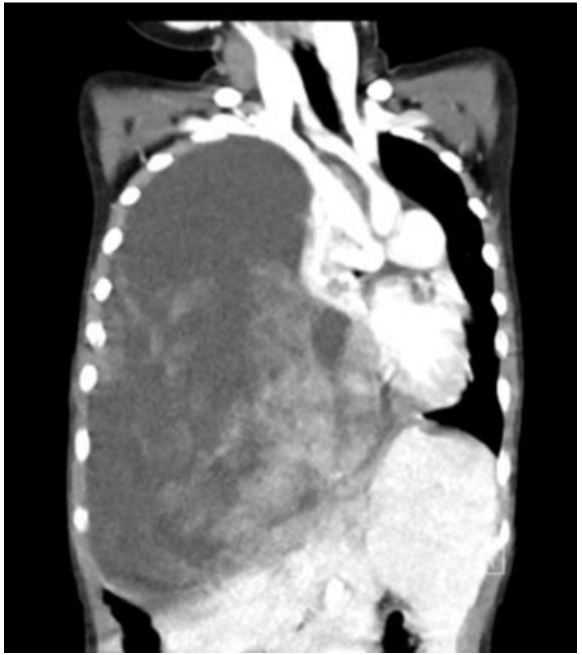
What is the prognosis of recurrent PPB?

What is the role of novel therapies in recurent PPB?

CASE REPORT | Med Arch. 2021;75: 61-65

Case presentation (3)

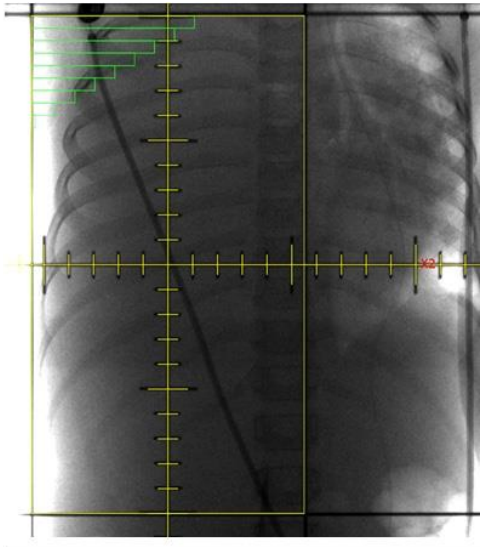
- A 6-year-old girl right upper lobectomy for type II PPB in May 2015
  - fever, cough, sputum, and dyspnea from 10 days ago
  - upper respiratory infection, no improvement
- referred to the emergency department
  - tachypnea and wheezing
  - right lung total collapse on chest X-ray
- Chest computed tomography (CT): 22.3 × 13.2 × 12.7 cm^3 sized cystic and solid mass in the right hemithorax



Radiation Oncology Journal 2020;38:148-150.

Case presentation

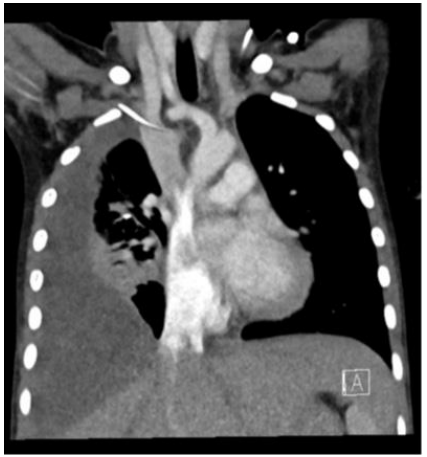
- disease-free interval of 4 years,
- PPB recurred with rapid progression.
  - atria collapse
  - compression superior and inferior vena cava
- IVADo regimen to relieve vascular obstruction
  - 2 days after chemotherapy, transferred to a PICU for
  - respiratory failure and obstructive shock with tumor progression.
- Radiotherapy
  - anteroposterior/posteroanterior field (11 × 20 cm2) weighted 1:1 to a total dose of 20 Gy in 4 fractions using 10 MV photon

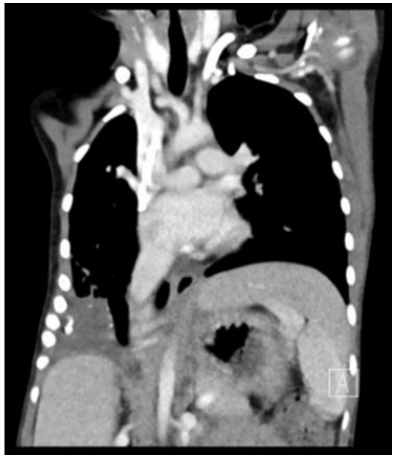


Radiation Oncology Journal 2020;38:148-150.

Therapy

- One week after RT: extubation
- one month without any further chemo- or radiotherapy,
  - the cystic and solid mass in the right hemithorax markedly reduced to 6.5 × 6.2 × 5.3 cm^3 in chest CT
- stable respiratory status in room-air
- 9 months after RT: 3.5 × 3.1 × 2.5 cm^3 in the last follow-up chest CT
- 4 pulse VAC (vincristine, actinomycin D, and cyclophosphamide)
- needle biopsy: only fibrous tissues
- next-generation sequencing analysis: DICER1 mutation (previous sample)





Radiation Oncology Journal 2020;38:148-150.

Case presentation #3: conclusion

- Recurrent type II PPB, DICER 1 positive

What is the role of radiotherapy in PPB?
Is PPB radiosensitive?

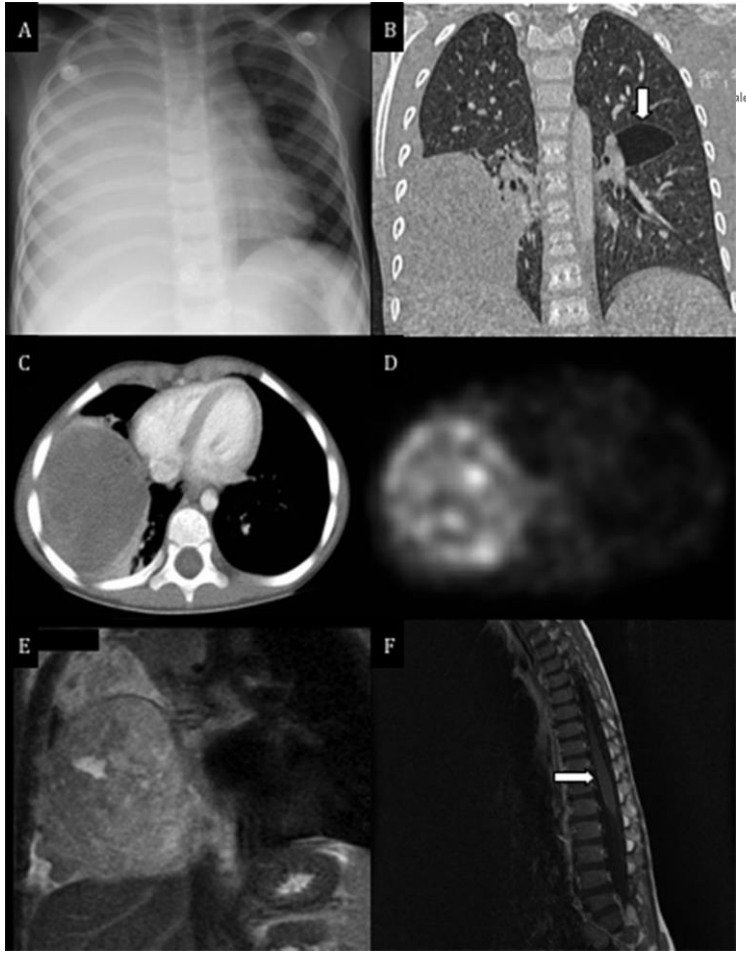
What is the role of genetic predisposition in PPB?

What is the prognostic implication of DICER 1 positivity?
Prognostic significance of DICER 1 in irradiated patients

Radiation Oncology Journal 2020;38:148-150.

Case presentation (4)

- 3-year-old previously healthy male
- Persistent cough and fever
- Absence of respiratory sounds on the right hemithorax
- X-ray, Ct- scan, PET-scan, MRI
  - Coronal chest CT scan (lung window) showing a solid mass in the right middle and lower lobes with short pleural effusion. Parahilar left cystic lesion
- Core needle biopsy consistent with type III PPB



Pediatr Blood Cancer 2017; 00: e26438

Therapy

- Enrollment in the International PPB Registry (IPPBR, http://www.ppbregistry.org)
- Neoadjuvant chemotherapy with ifosfamide, vincristine, actinomycin-D, and doxorubicin ("IVADo").
- remarkable objective volume shrinkage of the solid tumor was noticed after 12weeks of chemotherapy, → macroscopically complete resection.
- 24 additional weeks of ifosfamide, vincristine, and actinomycin–D (IVA)
- 1 year after primary diagnosis:
  - the left sided lung cystic lesion was surgically removed
    - pathological report : a 4 cm cystic formation, located in the peripheral portion of the lung parenchyma, showing internal epithelial lining and focally low cuboidal epithelium without signs of atypia.

Pediatr Blood Cancer 2017; 00: e26438

Therapy

- DICER1 gene sequence analysis revealed a germline heterozygous p.R688X mutation.
- Genetic testing from both parents and one sister was normal.
- Three additional small cystic lesions became apparent: one left para-hilar lesion of 18mm at the age of 4 years, and two lesions(3 and 7 mm) within the right upper lobe at the age of 5 years.

They decided to adopt a watch and wait policy and all these cystic lesions remained stable without further therapy

Six years after primary diagnosis the patient is alive and well.

Pediatr Blood Cancer 2017; 00: e26438

Case presentation #4: conclusion

- Type III pleuropulmonary blastoma in a DICER1 germline mutation carrier and residual lung cystic lesions

How would you manage this patient?

What is the role of surgical resection of cystic lung lesions in young children with PPB-tumor predisposition syndrome?

How should you follow-up these patients?

Pediatr Blood Cancer 2017; 00: e26438

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PLEUROPULMONARY BLASTOMA RECOMMENDATIONS

Arianna Tagarelli

16 February 2023

Funded by the European Union's EU4Health Programme

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St. Anna Kinderkrebs Forschung

PPB: Background

Very rare tumor which originates from either the lungs or pleura

It occurs mainly in children aged <5 years

Morphologically, PPB has three types : I cystic, II solid- cystic, III solid

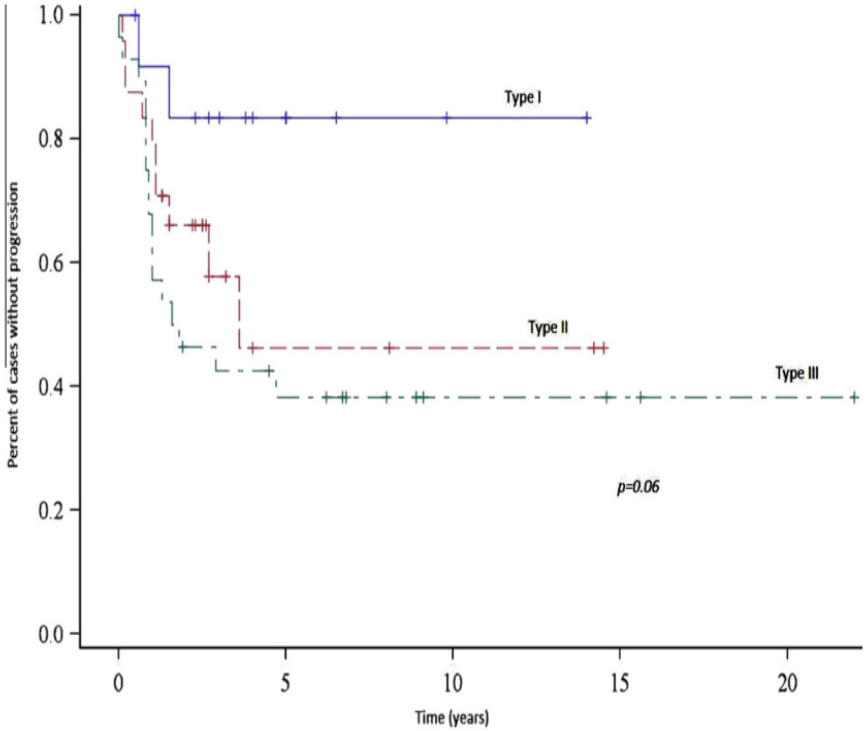
The progression from type I to type III is documented

Type II and III may show a mixed pattern including high grade sarcoma elements

DICER1 mutations are present in a majority of PPBs and may be part of a familial tumor predisposition syndrome.

5 year PFS

Type I: 89%
Type II: 45%
Type III: 38%



Bisogno et al, 2014

Current therapeutic guidelines were not well established until now, making treatment decisions and management difficult for clinicians

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Pediatric Blood & Cancer

SIOP INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY

aspho The American Society of Pediatric Hematology/Oncology

WILEY

SUPPLEMENT ARTICLE

Pleuropulmonary blastoma in children and adolescents: The EXPeRT/PARTNER diagnostic and therapeutic recommendations

Gianni Bisogno[1] | Sabine Sarnacki[2] | Teresa Stachowicz-Stencel[3] | V. Minard Colin[4] | Andrea Ferrari[5] | Jan Godzinski[6] | Marion Gauthier Villars[7] | Ewa Bien[3] | Frederic Hameury[8] | Sylvie Helfre[9] | Dominik T. Schneider[10] | Yves Reguerre[11] | Ricardo Lopez Almaraz[12] | Dragana Janic[13] | Maja Cesen[14] | Alexandra Kolenova[15] | Jelena Rascon[16] | Kata Martinova[17] | Rodica Cosnarovici[18] | Apostolos Pourtsidis[19] | Tal Ben Ami[20] | Jelena Roganovic[21] | Ewa Koscielniak[22] | Kris Ann P. Schultz[23] | Ines B. Brecht[24] | Daniel Orbach[25]

GENERAL RECOMMENDATIONS

- A tumor board discussion is highly recommended at diagnosis and during therapy.

- The enrolment of patients in a prospective trial if available and data collection in national or international databases should be proposed to patients and families

Staging investigations

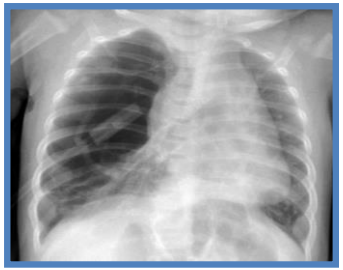
Chest Computed Tomography (CT) with contrast enhancement with extension to the abdomen for evaluation of diaphragm and liver.

Distant metastasis investigation should be searched in case of type II-III PPB:

- Brain MRI.
- Radionuclide Bone scan
- Echocardiography (for vascular invasion and intra-cardiac involvement).

Considered to look for synchronous DICER1-related disorders > abdominal ultrasound is recommended to exclude cystic nephroma and ovarian tumors (see genetic section).

TYPE I PPB: SURGERY



Cystic lung malformation/CCAM?

Initial tumor resection > thoracotomy is the recommended surgical approach

All residual disease should be resected to prevent later transformation to types II-III

TYPE I PPB: CHEMOTHERAPY

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Type I Pleuropulmonary Blastoma: A Report From the International Pleuropulmonary Blastoma Registry

John R. Priest, D. Ashley Hill, Gretchen M. Williams, Christopher L. Moertel, Yoav Messinger, Marsha J. Finkelstein, and Louis P. Dehner

A B S T R A C T

Purpose
Type I pleuropulmonary blastoma (PPB) is a rare, cystic lung neoplasm in infants characterized by subtle malignant changes and a good prognosis. Recurrences after type I PPB are usually advanced type II or type III neoplasms with a poor prognosis. This article describes the first collection of type I PPB cases, analyzes outcome based on treatments of surgery or surgery plus chemotherapy, and presents type I PPB management recommendations.

Patients and Methods
Type I PPB cases from the International PPB Registry and literature were evaluated using standard statistical methods for outcomes based on age at diagnosis, sex, thoracic side, surgical extent, length of follow-up, constitutional/familial disease, pre-existing lung cysts, intrathoracic findings, and treatments (surgery or surgery and chemotherapy).

Results
Thirty-eight type I PPB cases were identified: Registry (n = 30) and literature (n = 8). Twenty children had surgery alone; eight (40%) experienced recurrence; and four died. Eighteen children had surgery and adjuvant chemotherapy; one experienced recurrence and died. All recurrences were type II or III PPB. Recurrence-free survival was higher in the surgery + chemotherapy group ($P = .01$); overall survival did not differ ($P = .18$). The improved recurrence-free survival was found only in males. Four of nine children with recurrence survived.

Conclusion
Adjuvant chemotherapy appears to benefit type I PPB patients. Benefit limited to males requires broader substantiation. Salvage after types II and III recurrence is poor (four of nine; 44%). A rigorous surveillance schedule after type I PPB diagnosis might detect early recurre
acceptable alternative to adjuvant chemotherapy.

J Clin Oncol 24:4492-4498. © 2006 by American Society of Clinical Oncology

Adjuvant chemotherapy appears beneficial

TYPE I PPB: CHEMOTHERAPY

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for rare or low prevalence complex diseases

TABLE 1. Demographic, Treatment, and Outcome Data for Cystic PPB Types I and Ir

	Type I	Type Ir	Total Cystic PPB
Total, n (%)	89 (77)	26 (23)	115 (100)
Age at diagnosis (mo), median (range)	8 (0-114)	46.5 (7-546)	12 (0-546)
Sex, n (%)			
Female	38 (43)	7 (27)	
Male	51 (57)	19 (73)	
Pneumothorax, n (%)			
No	20 (22)	4 (15)	
Yes	29 (33)	5 (19)	
Unknown	40 (45)	17 (66)	
Anaplasia, n (%)			
Yes	4 (4)	0 (0)	
No	85 (96)	26 (100)	
DICER1, n/N (%)[a]			
Positive	17/28 (61)	4/6 (67)	
Negative	11/28 (39)	2/6 (33)	
Treatment, n (%)			
Surgery only	52 (58)	23 (88)	
Surgery with chemotherapy	29 (33)	3 (12)	
Surgery with unknown	8 (9)	0 (0)	
Follow-up (mo), median (range)	59.9 (0-477)	55.3 (0-472)	
Recurrence or progression[b]			
Recurrence (to type I or Ir), n (%)	[illegible]	1 (4)	
Progression to types II and III, n (%)	9 (10)	2 (8)	
Progression after surgery only, n/N (%)[c]	7/52 (12)	1 (4)	
Progression after surgery with chemotherapy, n/N (%)[c]	2/29 (7)	1 (33)	
Survival, n (%)			
Alive	84 (94)	26 (100)	
Dead	5 (6)	0 (0)	
5-year OS % (95% CI)	89 (80-99)	100	
5-year DFS % (95% CI)	79 (69-91)	93 (80-100)	

[a] The *DICER1* percentage was calculated only for the evaluated patients.
[b] The median time to progression was 23 mo (range, 3-53 mo).
[c] The progression percentage was calculated for patients treated with surgery only and for patients treated with surgery and chemot

Original Article

Pleuropulmonary Blastoma: A Report on 350 Central Pathology–Confirmed Pleuropulmonary Blastoma Cases by the International Pleuropulmonary Blastoma Registry

Yoav H. Messinger, MD[1]; Douglas R. Stewart, MD[2]; John R. Priest, MD[1]; Gretchen M. Williams, BS[1]; Anne K. Harris, MPH[1]; Kris Ann P. Schultz, MD[1]; Jiandong Yang, PhD[3,4]; Leslie Doros, MD[5]; Philip S. Rosenberg, PhD[6]; D. Ashley Hill, MD[3,4]; and Louis P. Dehner, MD[7]

TABLE 2. Prognostic Cox Hazard Model[a]

	Disease-Free Survival			Overall Survival		
Prognostic Factor	Types I and Ir	Type II	Types II/III and III	Types I and Ir	Type II	Types II/III and III
Upfront chemotherapy	.11	.06	.00007[b]	.63	.29	.17
Laterality	.12	.41	.94	.13	.96	.12
Pleural effusion	.13	.12	.33	.2	.13	.27
Sex	.14	.08	.33	.92	.03	.16
Tumor spillage	.17	.01[c]	.7	.47	.08	.57
Focality	.17	.41	.56	.46	.38	.52
Date of birth ≥ 2002	.25	.06	.41	.25	.12	.25
DICER1 mutation	.26	.94	.63	ND	.37	.91
Intrathoracic nodes	.47	.77	.86	.13	.2	.74
Upfront radiation	.48	.58	.32	.66	.38	.36
Lesion size	.52	.04	.84	.25	.26	.6
Pneumothorax	.55	.02[c]	.002[b]	.32	.04	.01[c]
Age at PPB diagnosis (4 steps)	.67	.03	.38	.61	.1	.42
Anaplasia	.12	.46	.38	.23	.68	.28
Distant metastasis	None	.002[d]	.0002[b]	None	.002[d]	.002[d]

Abbreviations: ND, not determined; PPB, pleuropulmonary blastoma.
[a] Cox models of prognostic factors are presented for disease-free survival and overall survival. Types I and Ir and types II/III and III are grouped together because of small numbers. Observed *P* values significant by the false discovery rate are flagged.
[b] $P < .01$.
[c] $P < .1$.
[d] $P < .05$.

European experience in PPB Type I Role of adjuvant chemotherapy?

Number	**13 ptsr**
TNM:	
T1	**12/13**
N0	**13**
M0	**13**

Therapy:

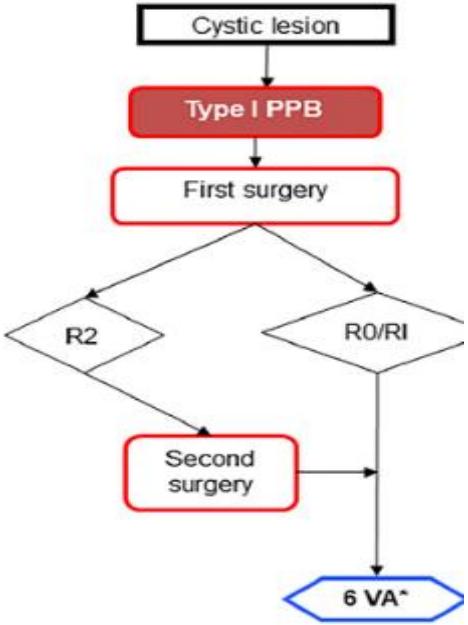
Treatment and prognostic factors in pleuropulmonary blastoma: An EXPeRT report

Gianni Bisogno [a,*], Bernadette Brennan [b], Daniel Orbach [c], Teresa Stachowicz-Stencel [d], Giovanni Cecchetto [e], Paolo Indolfi [f], Ewa Bien [d], Andrea Ferrari [g], Florence Dommange-Romero [h]

No adjuvant therapy: 6 pts R0 → 2 relapses
Adjuvant CT: 7 pts [6 R0, 1 R1] → 0 relapse

Survival:
5 Y PFS: 83.3% (48.2–95.6)
5 Y OS: 91.7% (53.9–98.8)

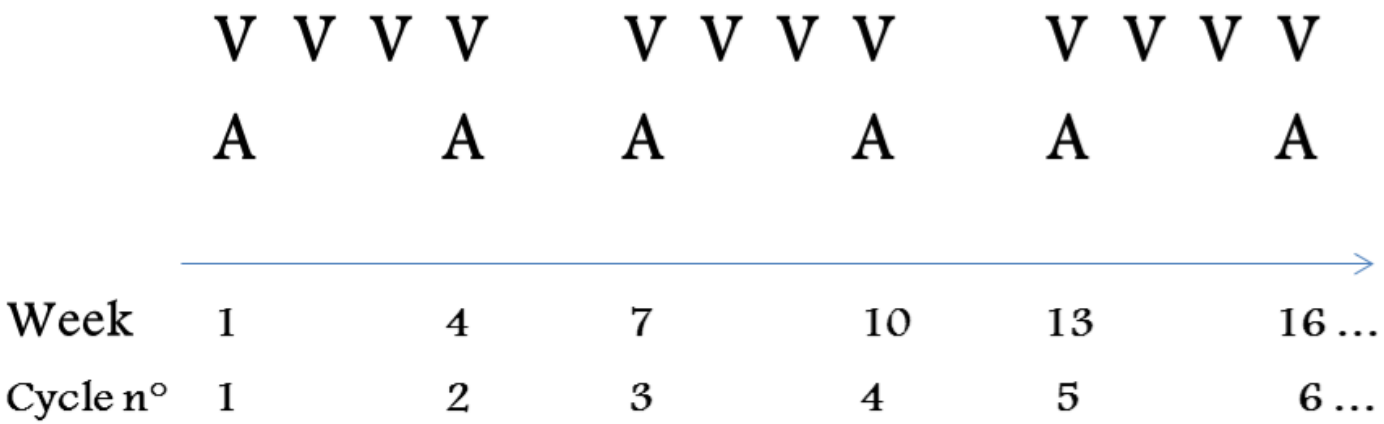
TYPE I PPB



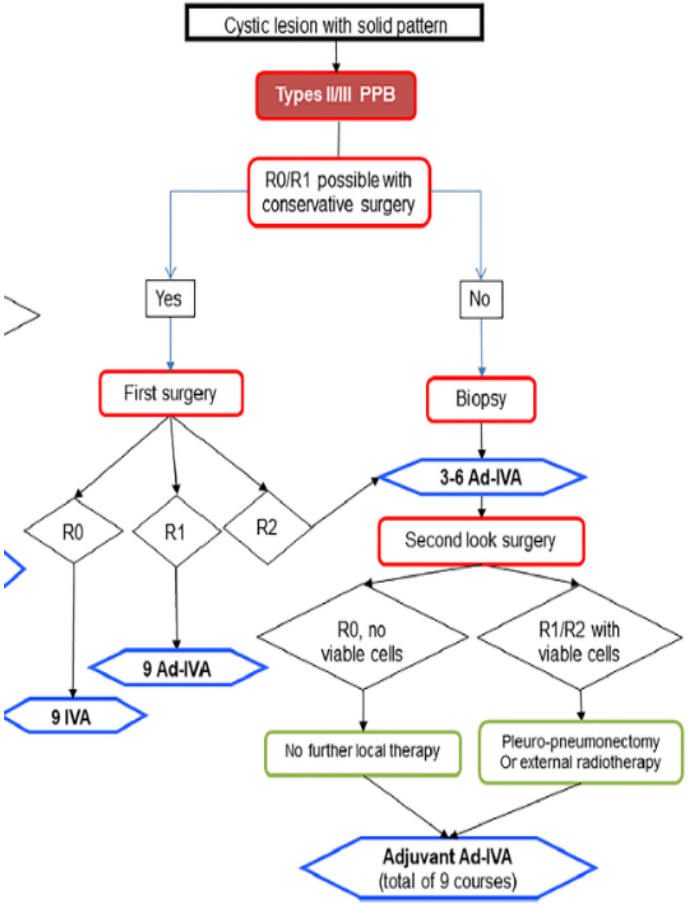
- Proposition: adjuvant therapy to try to avoid progression in Types II-III.
- Chemotherapy maybe avoided for complete surgery (R0 resection), but is strongly recommended for any other situations
- chemotherapy with 6 courses of VA is recommended

CT regimen

VA regimen (Vincristine + Actinomycin-D)



Type II/III PPB



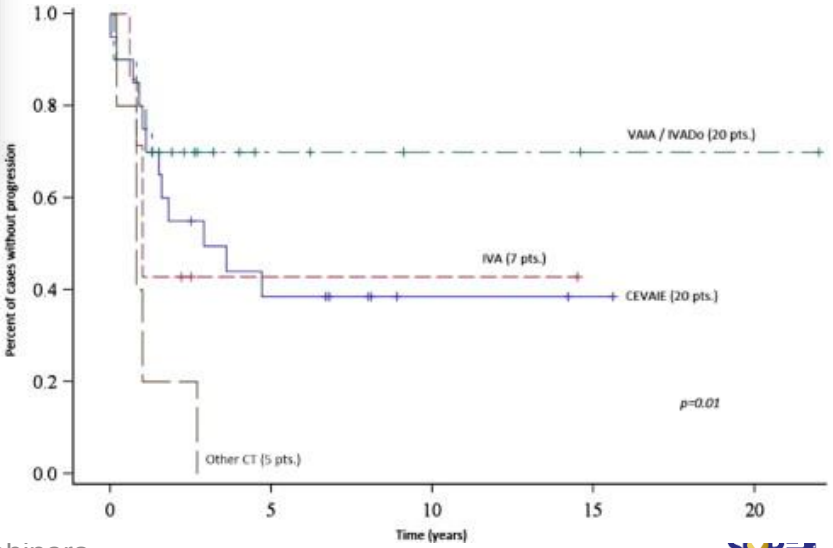
All patients with
types II-III PPB
should receive chemotherapy

Different multidrug regimens with evidence of tumor response have been described

Some data seem to support the use of a doxorubicin-containing regimen

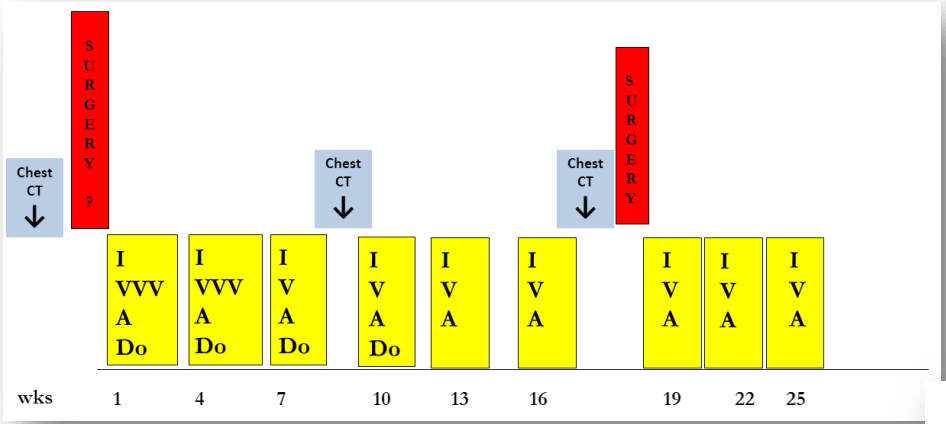
Treatment and prognostic factors in pleuropulmonary blastoma: An EXPeRT report

Gianni Bisogno [a,*], Bernadette Brennan [b], Daniel Orbach [c], Teresa Stachowicz-Stencel [d], Giovanni Cecchetto [e], Paolo Indolfi [f], Ewa Bien [d], Andrea Ferrari [g], Florence Dommange-Romero [h]



VAIA or IVADo 5-year PFS of 70% versus 31.3 for all the other regimens

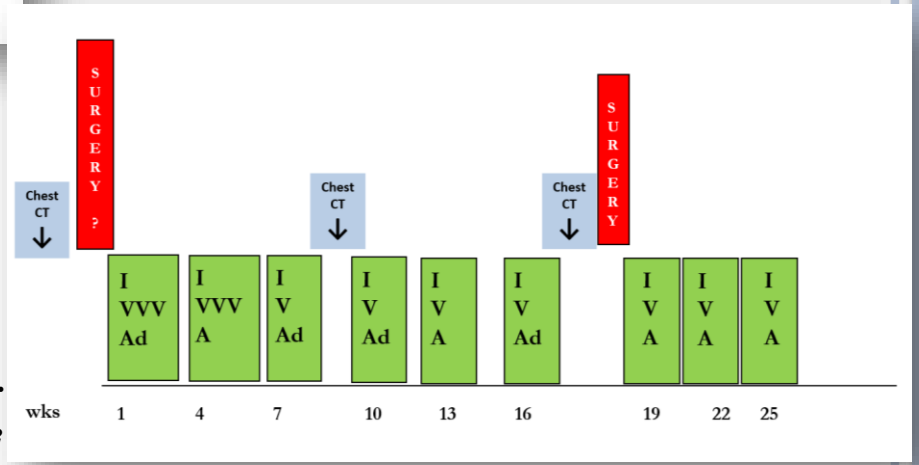
CHEMOTHERAPY SCHEDULE FOR TYPES II-III PPB



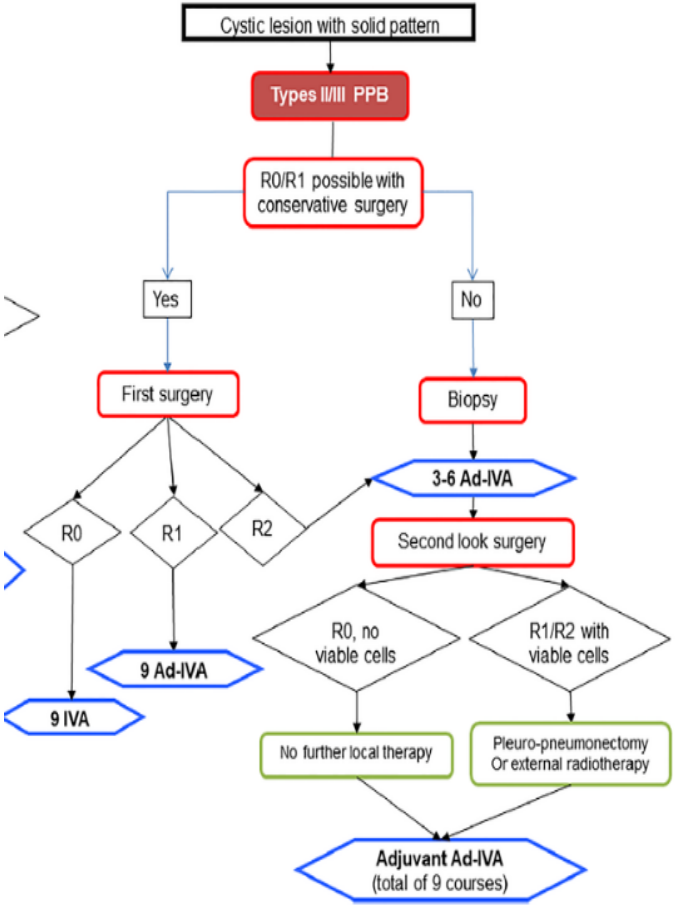
Doxorubicine:
4 x 60 mg/m²

IVADo regimen (Expert group)

VAIA regimen



Doxorubicine:
4 x 80 mg/m²



Role of radiotherapy

- The role of external **radiotherapy** is unclear in PPB.
- Deliver radiotherapy only in the case of residual tumor after chemotherapy that contains viable cells incompletely resected despite a second look surgery.
- Total dosage between 45 Gy (R1 margins) to 54 Gy (R2 margins).

OVERALL STRATEGY IN PPB – EXPERT PROPOSAL

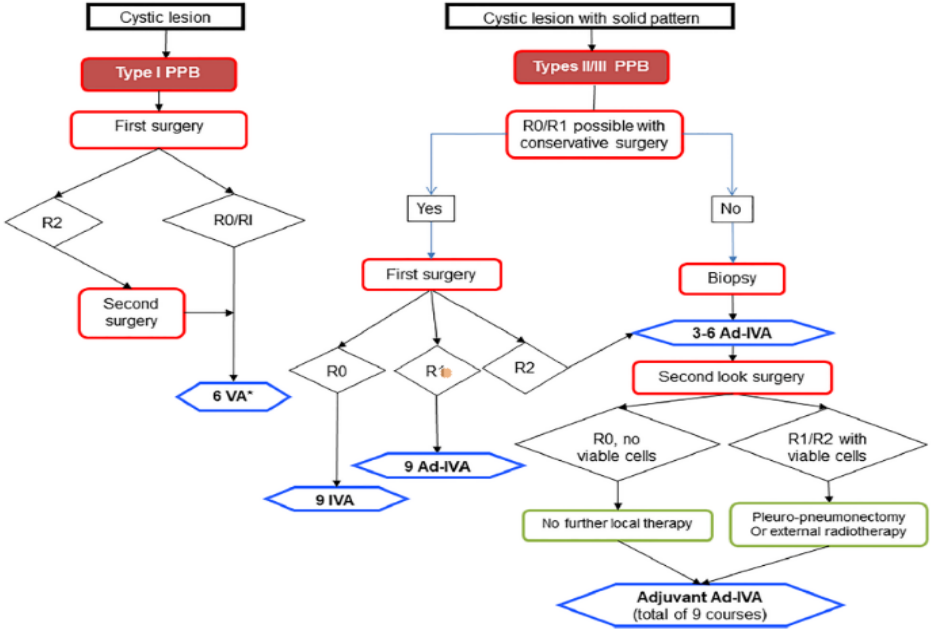


FIGURE 1 The therapeutic strategy proposed by EXPeRT-PARTNER (European Cooperative Study Group for Pediatric Rare Tumors within the European Union-funded project Paediatric Rare Tumours Network - European Registry) for pleuropulmonary blastoma. Abbreviations: R0, complete delayed surgery; R1, microscopic incomplete delayed surgery; R2, macroscopic incomplete delayed surgery. Ad-IVA: IVAdo/IVA or VAIA regimens. *The decision for chemotherapy versus observation after surgery for Type I pleuropulmonary blastoma (PPB) depends on a variety of factors

Back to the cases

Case n. 1 Pre adolescent female with PPB type Ir completely resected at diagnosis

What is the difference between PPB type I and PPB type Ir ?

How would you treat and follow up a type I and type Ir PPB?

What is the prognosis of type I and type Ir PPB?

Type I/Type IR

ORIGINAL ARTICLE

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

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Type Ir is a purely cystic tumor which does not have a primitive cell component

The 5-year overall survival rate for type I/Ir PPB patients is 91%, but 10% may later progress to type II or III.

In the latest IPPBR study that included 26 patients with PPB type Ir, 4% had disease recurrence and 8% progressed to type II/III

Case n. 2 Infant with recurrent disease and a type II PPB

What is the prognosis of recurrent PPB?

What is the role of novel therapies in recurent PPB?

How would you treat this patient?

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Pediatric Blood & Cancer

ONCOLOGY: RESEARCH ARTICLE

Children with progressive and relapsed pleuropulmonary blastoma: A European collaborative analysis

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Clinical characteristics

	Progressive Disease	Relapsed Disease
Number of patients	9	26
Median age	3.9	4.3
Type III	All	16 (65%)
IRS	II (1), III (6), IV (2)	I (4), II (5), III (12), IV (5)
First line CHT	ALL	ALL

Progressive disease: local control in 4 cases, all died

Relapsed disease: patients were treated with salvage CHT (n=20), surgery (n=10), and/or RT (n=10).

Patient, IRS-group at initial diagnosis, Dehner classification	Location of RD	First line CHT	Response	Time of RD after initial diagnosis	Second line CHT	Tumor response to second line CHT	Salvage secondary surgery/ RT	Follow-up from diagnosis of relapse (years)	Outcome
1, II, Type 3	CNS	IVA	PR	0.9	carboplatin/VAC, cisplatin/doxorubicine	PR	no/no	2.1	DOD
2, III, Type 3	CNS	IVaDo	Minor PR	0.7	carboplatin/etoposide	PD	yes/no	0.4	DOD
3, III, Type 2	local	VAC	CR	1.9	ICE	PD	no/yes	0.3	DOD
4, IV, Type 2	local	IVA	n.a.	1.0.	carboplatin/ etoposide	PD	yes/yes	7.1	2nd relapse: Adriamycin, cisplatine, etoposide: PR, then CR; ACR1
5, II, Type 3	local	IVA	n.a.	1.0	carboplatin/ etoposide	CR	no/no	0.8	DOD
6, IV, Type 3	CNS, Orbital	CEVAIE, O-TIE	n.a.	0.0.	topotecan/cyclophosphamide	PD	no/no	0.9	DOD
7, III, Type 2	local	VAIA, O-TIE	CR	1.8	carboplatin/etoposide/ cyclophosphamide	PD	yes/no	0.9	DOD
8, I, Type 3	CNS	VAIA	n.a.	0.5.	PEI (cisplatin, etoposide, ifosfamide)	PD	no/no	0.1	DOD
9, IV, Type 3	CNS	CEVAIE, O-TIE	n.a	1.4	irinotecan/temodal	PR	yes /no	1.0	Alive with residue
10, II, Type 2 (after initial Type1)	local	IVADo	CR	1.8	carboplatin/etoposide/ cyclophosphamide	PR	yes/yes	9.1	ACR2
11, IV, Type 3	Local, bone	IVADo, CYC/VNB	PR on PT	1.2 CR on bone metastasis	ICE and carboplatin/etoposide/cyclophosphamide	PR	yes/yes	3.1	2nd relapse, targeted treatment, Alive on therapy

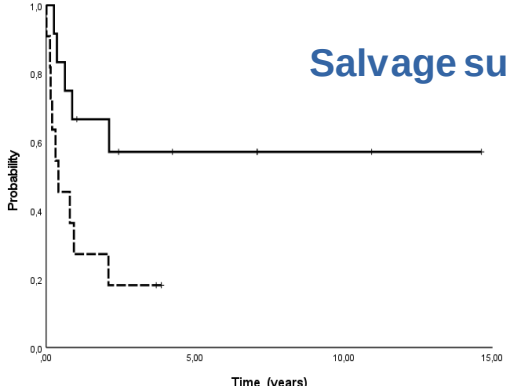
CT Carbo VP16

Irinotecan/TMZ/Cyclo

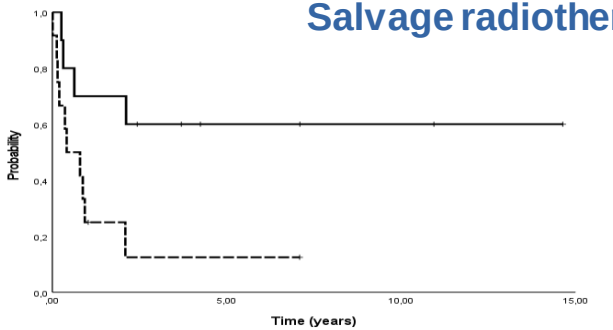
Multidrug/Doxo

Prognostic factors

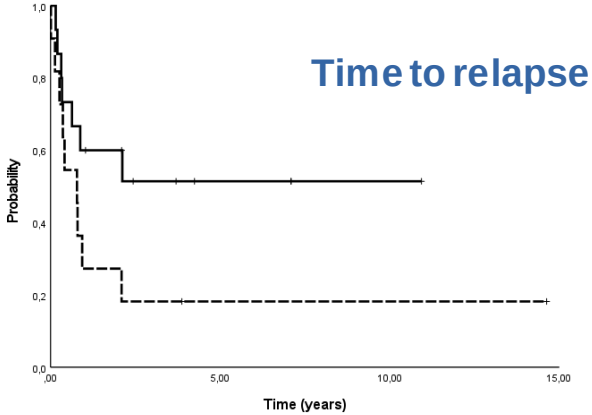
Salvage surgery



Salvage radiotherapy



Time to relapse



poor prognosis BUT patients with relapse may have a chance

Local control is important

New therapy is warranted for these patients

International collaboration is mandatory

Case n.3 Recurrent type II PPB, DICER 1 positive

What is the role of radiotherapy in PPB? Is PPB radiosensitive?

What is the role of genetic predisposition in PPB?

What is the prognostic implication of DICER 1 positivity and irradiated patients?

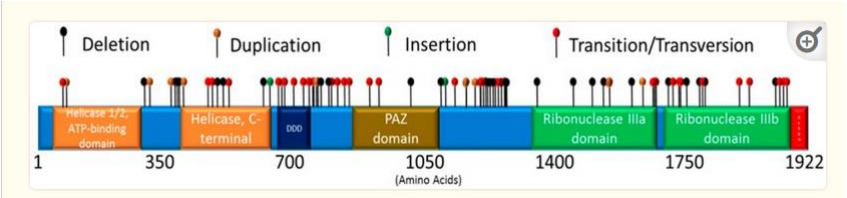
Radiotherapy

- Radiotherapy is **not recommended** for PPB **type I**.

- We recommend radiotherapy only in the case of **residual viable tumor** after chemotherapy and second look surgery in **PPB type II-III.**

- Specific attention should be paid to potential long-term side effects of myocardial irradiation after anthracycline exposure.

GENETIC CONSIDERATIONS



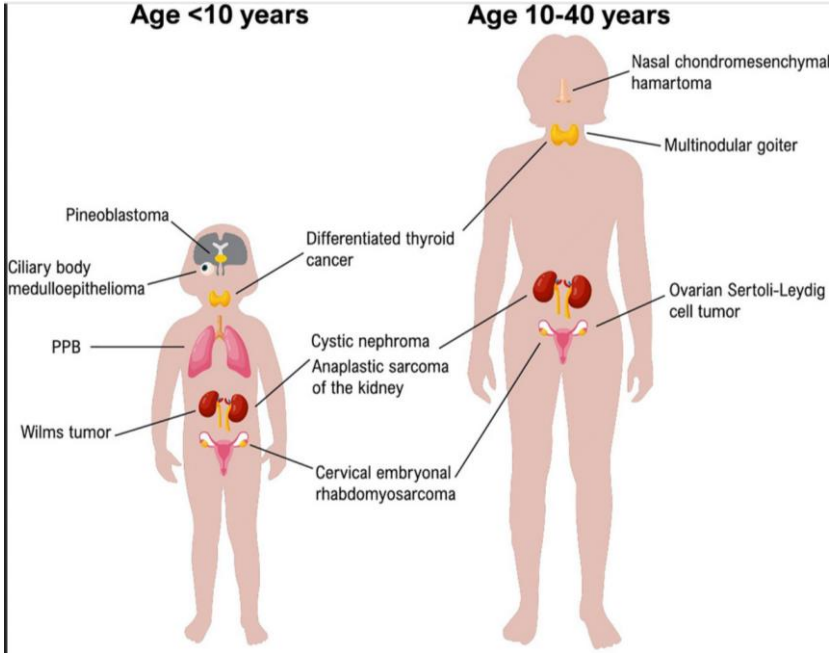
DICER1 Pathogenic Germline Mutations. Mutations reported in *DICER1* include deletions, duplications, insertions, transitions, or transversions. The *DICER1* gene encodes 1922 amino acids, arranged into specific domains including the helicase 1/2, ATP-binding domain, the helicase, C-terminal domain, the Dicer dimerization domain (DDD), the PAZ domain (PAZ), the ribonuclease IIIa domain, and the ribonuclease IIIb domain. (see Tables 1–3).

DICER1 syndrome is a rare genetic condition predisposing to hereditary cancer

many individuals who carry a mutation in the DICER1 gene do not develop abnormal growths >> second mutation

Prevalence of DICER1 syndrome is currently unknown

The full spectrum of clinical manifestation may not yet be fully defined



GENETIC CONSIDERATIONS

Genetic counselling should be proposed to all patients with PPB and their family

Radiological and clinical screenings in case of *DICER$_1$* mutation recommendations are not validate

Overall **recommendations** in patients with constitutional *DICER$_1$* mutation:

Chest X-Ray at birth, then every 4 months until 6 years with an additional low dose thoracic CT scan at 6 months of age,

Abdominal pelvic and abdominal US at birth for all; and every year in female since 10 years of age,

Clinical cervical examination every year

Thyroid palpation yearly

Case n.4

Type III pleuropulmonary blastoma in a DICER1 germline mutation carrier and residual lung cystic lesions

How would you manage this patient?
What is the role of surgical resection of cystic lung lesions in young children with PPB-tumor predisposition syndrome?
How should you follow-up these patients?

Challenging situation

Surgical resection is recommended when feasible

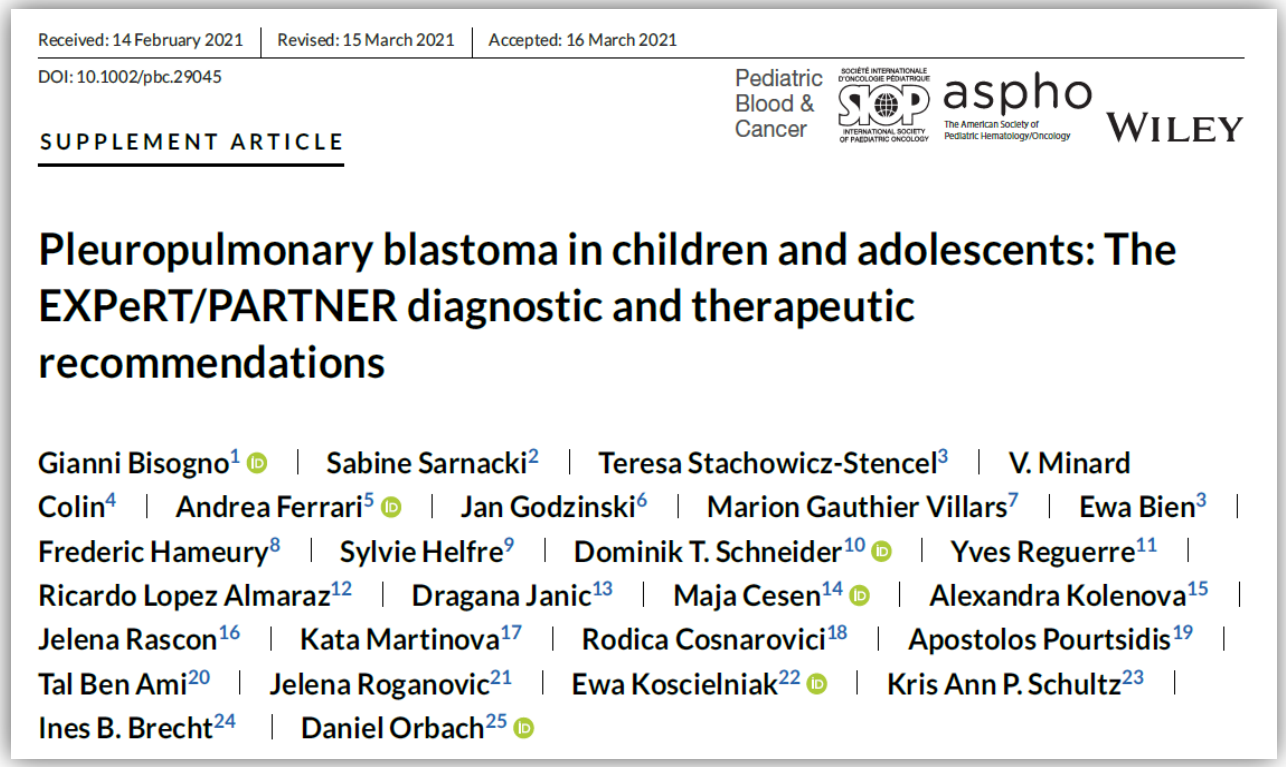
Aggressive surgical Approach >> complications

Not all cysts are malignant

Many questions still open….

- Best timing for delayed surgery in type II-III: early or not?
- Role of radiotherapy in type II-III with residual disease after surgery?
- Indication, fields and dosages of radiotherapy?
- Treatment of poor responders, metastatic or relapsed tumors
- Efficacy of new drugs in PPB: topotecan?

Thank you



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Pediatric Blood & Cancer

SUPPLEMENT ARTICLE

Pleuropulmonary blastoma in children and adolescents: The EXPeRT/PARTNER diagnostic and therapeutic recommendations

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