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SUPPLEMENT ARTICLE

Pancreatoblastoma in children: EXPeRT/PARTNER diagnostic and therapeutic recommendations

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Abstract

Pancreatoblastoma (PBL) is a rare malignant epithelial neoplasm that affects typically young children. Signs related to advanced upper-abdominal tumor accompanied by elevated serum α-fetoprotein levels in a young child suggest PBL, however histopathological confirmation is mandatory. The mainstay of the treatment is a complete surgical resection. Unresectable and/or metastatic PBL may become amenable to complete

Abbreviations: AFP, α-fetoprotein; CT, computed tomography; EFS, event-free survival; EXPeRT, European Cooperative Study Group for Pediatric Rare Tumors; FAP, familial adenomatous polyposis; FDG-PET, 18F-fluorodeoxyglucose-positron emission tomography; ICE, ifosfamide, carboplatin, and etoposide; IGF-2, insulin-like growth factor 2; MIS, minimally invasive surgery; MRI, magnetic resonance imaging; NSE, neuron-specific enolase; OS, overall survival; PARTNER, Paediatric Rare Tumours Network - European Registry; PBL, pancreatoblastoma; PLADO, cisplatin and doxorubicin; RT, radiotherapy; US, ultrasound; VAC, vincristine, actinomycin D and cyclophosphamide; VRT, very rare tumors

delayed surgery after neoadjuvant chemotherapy. This manuscript presents the international consensus recommendations for the diagnosis and treatment of children with PBL, established by the European Cooperative Study Group for Pediatric Rare Tumors (EXPeRT) within the EU-funded PARTNER (Paediatric Rare Tumors Network – European Registry) project.

KEYWORDS
children, diagnosis, EXPeRT, pancreatoblastoma, PARTNER, recommendations

1 | INTRODUCTION

Pancreatoblastoma (PBL) is a rare malignant pancreatic neoplasm, originating from the epithelial exocrine cells of the pancreas. It affects mainly children under 10 years of age, with a mean age at diagnosis of 5 years.[1] It is the most common malignant pancreatic tumor in childhood, constituting approximately 25% of all tumors of pancreas in young children and 0.5% of all pancreatic exocrine neoplasms.[2] PBL has a bimodal distribution with two thirds of cases occurring in children and one third in adults.[2–5] A joint analysis of the European Cooperative Study Group for Pediatric Rare Tumors (EXPeRT) group collected only 20 children with PBL treated between 2000 and 2009 in Italy, France, Germany, Great Britain, and Poland.[6]

The etiology of PBL is unknown. The association with hereditary syndromes such as Beckwith–Wiedemann or familial adenomatous polyposis (FAP) has been reported. The prevalence of Beckwith–Wiedemann syndrome is particularly high (50%) in children with congenital and infantile PBL, compared to 4.5% in all PBL patients.[7] Sporadic and FAP-associated PBL have frequent alterations in the adenomatous polyposis coli (*APC*)/beta-catenin (*CTNNB1*) pathway and allelic loss in chromosome 11p.[8] The latter finding together with the overexpression of insulin-like growth factor 2 (IGF2) and frequent expression and secretion of α-fetoprotein (AFP) represent the similarities between PBL and hepatoblastoma.[5,8]

PBL can arise from any part of the pancreas, most commonly within the head or tail. It is an aggressive tumor, which is usually diagnosed at advanced stages. Approximately, one third of cases in all age groups initially present with locoregional and distant metastases, mainly to the liver, abdominal lymph nodes, and lungs.[9]

Children often present with upper abdominal pain, vomiting, feeding disorders, and weight loss.[2,10] Symptoms resulting from obstruction of the biliary tract or pancreatic duct are less frequent than in adults who mainly present with tumors in the pancreatic head. In a small proportion of patients, a firm palpable mass and/or fullness are present in the upper abdomen. Diagnostic difficulties and/or delays may result from nonspecific clinical symptoms and the extreme rarity of this disease.[6,11–14] However, elevated levels of AFP in serum of a young child with large pancreatic mass should highly suggest PBL.[15]

Histology is essential for the diagnosis of PBL. Histological specimens typically reveal multiple lines of differentiation (acinar, ductal, mesenchymal, neuroendocrine), with acinar differentiation predominating. The presence of squamoid nests is specific for PBL and indicates a growth pattern, not a line of differentiation.[16] PBL in young children should be differentiated from a variety of benign pancreatic lesions, other primary malignant tumors and/or secondary neoplastic infiltration. The differential diagnosis is based on age, clinical presentation, radiologic findings, serum level of AFP, and finally the pathologic features of the tumor sample.[5,17]

Mainstay of the treatment is a complete resection, either primary or following neoadjuvant chemotherapy. PBL is considered sensitive to chemotherapy. The response rate to conventional chemotherapy regimens in the EXPeRT series of 20 pediatric PBL cases was 73%.[6] However, standardized treatment guidelines have yet to be determined.

The prognosis for pediatric PBL cases is usually favorable if the tumor is completely resected, either on primary or delayed surgery.[1,2,5,6,11,12,14] In the EXPeRT series, 5-year event-free survival (EFS) and overall survival (OS) were 58.8% ($\pm$12.5%) and 79.4% ($\pm$9.2%), respectively.[6] Congenital and infantile PBL are associated with particularly good prognosis.[5,7] The recurrence rate after complete tumor resection in patients with PBL is lower than reported previously (14.7% vs. 60.0%).[5] However, close and long-term follow-up is necessary, especially in genetically susceptible patients with the pancreas remaining after surgery. In case of unresectable tumor or in the presence of metastases, PBL may have an aggressive course and the prognosis is usually poor.[12,14] As mentioned, the outcomes improve in patients in whom the tumors respond well to neoadjuvant chemotherapy and become feasible to complete delayed surgery.[6] Adult cases are reported to have an aggressive behavior and poorer prognosis with a median OS of approximately 15 months.[18–24]

The aim of this article is to establish internationally recognized recommendations for the diagnosis and treatment of children with PBL according to the Consensus Conference Standard Operating Procedure methodology with definition of levels of evidence (Levels I to V) and grades of recommendation (Grades A to E)[25] (Table 1). The methodology of the process – development under the auspices of the European Reference Network for Paediatric Cancer (ERN PaedCan) is described in the paper by Orbach et al. in this issue.[26]

TABLE 1 Consensus Conference Standard Operating Procedure methodology with definition of levels of evidence and grades of recommendation

Levels of evidence	
I	Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
II	Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, expert opinions
Grades of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, …), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

2 | EXPeRT/PARTNER RECOMMENDATIONS FOR MANAGEMENT OF PBL IN CHILDREN

2.1 | Initial tumor assessment

PBL should be suspected when a child presents with a large mass located in the pancreas, particularly when serum AFP levels are elevated (Level IV; Grade B). Differential diagnosis should exclude other primary malignant pancreatic tumors (endocrine tumors, acinar cell carcinomas, sarcomas) and benign lesions (hemangiomas, cysts, pseudocysts, and abscesses). Furthermore, the infiltration of the pancreas by leukemia or lymphoma must also be considered. Early childhood malignancies, such as neuroblastoma, nephroblastoma, and hepatoblastoma, should be included in the differential diagnosis, especially for tumors displacing, distorting, and/or disrupting normal pancreatic architecture on radiographic evaluation.[27] In older children, PBL should be differentiated from other pancreatic tumors, such as solid pseudopapillary tumor that occurs mainly in female adolescents, pancreatic malignant neuroendocrine neoplasms, and, in adults, acinar cell carcinoma or adenocarcinoma. Analysis of the imaging studies, detection of elevated AFP in serum, and characteristic histological findings of acinar differentiation and squamoid corpuscles in histopathologic examination help to diagnose PBL accurately.

2.1.1 | Radiological investigations

An appropriate cross-sectional imaging performed at diagnosis is essential to assess PBL stage.[5,17,28] Locoregional evaluation should include abdominal ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI) (Level IV; Grade A). On US, PBL presents as a large, solitary, well-defined, multilobulated lesion of mixed echogenicity located within the pancreas, mainly in the head and tail (Level IV; Grade B). Necrosis, hemorrhage, dilatation of the pancreatic and/or bile ducts (intra- and/or extrahepatic), local and vascular infiltration, lymphadenopathy, liver metastases, or other adjacent organs invasion can be identified.[29] Since exact anatomical margins of pancreatic tumor, especially in relation to adjacent organs, may be difficult to assess on US, when PBL is suspected, CT or MRI is mandatory for precise staging (Level V; Grade B). Abdominal CT with multiphase intravenous and enteral contrast shows heterogenous enhancement, particularly visible in the septae of the tumor, and simultaneous solid and cystic areas within the tumor. On parenteral contrast-enhanced abdominal MRI, the necrotic and hemorrhagic components are visualized in T2 sequences. Macroscopically, PBL usually presents as a large (frequently more than 10 cm in diameter), partially encapsulated, and often lobulated mass.[12] PBL developing in neonates and associated with Beckwith–Wiedemann syndrome is often cystic.[39] PBL is frequently found compressing the nearby organs without invading them; hence cross-sectional imaging is of utmost importance to define visceral and vascular involvement and relationship, especially for preoperative planning. Dilatation of the choledochal duct is rare. Preoperative endoscopic retrograde cholangio-pancreatography (ERCP) is indicated if there is a dilatation of the common bile duct or pancreatic ducts (Level V; Grade B). Contrast-enhanced MRI cholangiopancreatography may obviate the need for a dedicated endoscopic procedure unless tissue sampling is required and/or further definition with an endoscopic US is mandated to better define the margins of resection preoperatively.[28]

Metastatic lesions are most frequently located in the liver, regional lymph nodes, and lungs. For the visualization of metastases, abdominal US, contrast-enhanced CT, and/or MRI and chest CT are required (Level IV; Grade A). MRI has become the cross-sectional modality of choice for the evaluation of pediatric liver masses both primary and metastatic. The incorporation of multiphase contrast agent-enhanced evaluation enables the accurate visualization and characterization of liver lesions without additional radiation exposure.[30] This advantage of MRI may assist to detect liver metastases in PBL. Bone metastases

TABLE 2 Current classification of pancreatic cancers based on the 8th edition of the AJCC Cancer Staging Manual (2018)

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor limited to the pancreas, 2 cm or less in greatest dimension
T2	Tumor limited to the pancreas, more than 2 cm in greatest dimension
T3	Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery
T4	Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
Anatomic stage/prognostic groups in pancreatic cancer	
Stage 0	Tis N0 M0
Stage IA	T1 N0 M0
Stage IB	T2 N0 M0
Stage IIA	T3 N0 M0
Stage IIB	T1 N1 M0
	T2 N1 M0
	T3 N1 M0
Stage III	T4 any N M0
Stage IV	Any T any N M1

are rare. If suspected, the technetium bone scan might be performed, but this may be deferred in lieu of the results that can be obtained from a 18F-fluorodeoxyglucose (FDG)-positron emission tomography (PET) scan (Level V; Grade C). Recently, pediatric PBL and retroperitoneal lymph nodes metastases have been reported to show elevated uptake of FDG in FDG-PET scans.[31,32] However, the diagnostic utility of FDG-PET scanning to differentiate benign from malignant pancreatic tumors in children and for the initial workup is yet to be established (Level V; Grade C).

2.1.2 | Tumor markers

Initial diagnostic workup should include the serum level of AFP (Level IV; Grade A), in addition to other serum tumor markers associated with pancreatic endocrine tumors (glucose, insulin, gastrin, glucagon), neuroblastoma (ferritin, neuron-specific enolase [NSE]), and/or germ cell tumors (beta subunit of human chorionic gonadotropin), which may mimic PBL. AFP is elevated in up to 70% of patients with PBL regardless of age.[9] In infants, AFP must be evaluated in comparison to age-related reference levels.[33] AFP level might also serve as a marker for monitoring the response to chemotherapy, since it is generally correlated to the tumor burden.[6,34–36]

2.2 | Staging system

The tumor, node, metastasis (TNM) classification of the American Joint Committee on Cancer (AJCC) is usually used to determine the staging of pancreatic tumors in adults (Table 2).[37] Since a staging system tailored specifically to PBL does not exist, a clinical-pathologic staging system based on the results of initial surgery is proposed by EXPeRT members to allow comparisons (Table 3).

2.3 | Histological diagnosis

Histology is mandatory to establish a diagnosis of PBL and distinguish it from other malignant or benign conditions involving pancreas (Level IV; Grade A). A revision of the histological slides by a

TABLE 3 Staging system for pancreatoblastoma (PBL) based on the results of initial surgery proposed by EXPeRT

Stage I	Completely excised localized tumors with negative microscopic margins (R0) and no evidence of LN on pathological evaluation (N0)
Stage II	Grossly resected tumors with suspected microscopic residual disease (R1); or completely resected (R0) but pathologically involved lymph nodes totally resected (N1)
Stage III	Gross residual disease after initial incomplete resection or biopsy (R2) regardless of LN involvement
Stage IV	Presence of distant metastases (M0) regardless of resection status (R0–R2) or lymph node involvement (N0–N1)

pathologist with proven experience in pediatric tumors and especially tumors of pancreas is highly recommended (Level IV; Grade B). Diagnostic biopsies can be obtained by different approaches (percutaneous image-guided tru-cut biopsy, endoscopic esophago-gastro-duodenoscopy (EGD)/endoscopic ultrasound (EUS) – core needle biopsy, and laparoscopic or open surgical biopsy). The aim is to ensure an adequate specimen for correct diagnosis, with the minimal invasiveness for the patient. For these purposes, the biopsy of a metastatic site, instead of the primary, is acceptable (Level IV; Grade B).[38] Also, an open question remains regarding the risk of tumor spillage in the case of initial transperitoneal biopsy of PBL. Therefore, it might be reasonable to consider posterior instead of transperitoneal biopsy access. A biopsy should provide enough tissue for histological and biological genetic tests. It is strongly recommended to store a frozen tumor sample and a blood sample on ethylenediaminetetraacetic acid (EDTA) in a tumor bank for possible subsequent biological studies, including genetics (Level V; Grade B).

Histological evaluation demonstrates lobules and nests of acinar and gland-like cell formations, together with squamoid cell nests.[40] Low-power appearance resembles lymphoid follicles. There are often small pseudocysts or areas of hemorrhage and necrosis, typically with calcifications. Pediatric cases often have hypercellular stroma, occasionally with bone and/or cartilage elements.[16] Immunohistochemistry is usually strongly positive for cytokeratin AE1/AE3, and often positive for carcinoembryonic antigen (CEA). Acinar regions show positive immunostaining for trypsin and chymotrypsin, while solid regions for AFP. Squamoid morules are positive for epithelial membrane antigen (EMA) and show aberrant reaction (nuclear or cytoplasmic) with beta-catenin. Staining toward neuroendocrine markers is negative in most cases and only occasionally, neuroendocrine component immunoreactivity for S-100, chromogranin, synaptophysin, and NSE is observed.[41] The proliferative activity is between <1 and 42 mitoses per high power field (HPF). Nuclear polymorphism is low, and tumor cell invasion in perineural spaces and vessels is rare. In most cases, expression and secretion of AFP can be observed.[9,34,42,43]

2.4 | PBL treatment

Patients should be treated in qualified centers, and multidisciplinary team discussions are mandatory at diagnosis, during therapy, and for ongoing surveillance (Level IV; Grade A). An enrollment in a prospective trial if available and data collection in national or international databases should be proposed (Level IV; Grade B).

2.4.1 | Surgery

Surgery is the cornerstone of treatment. The goal is to obtain a microscopically complete resection (negative margins, R0), which significantly improves the prognosis.[44] Achieving safe tumor-free margins is crucial, as relapses are likely to occur after incomplete surgery (positive microscopic [R1] or macroscopic [R2] margins), despite adjuvant chemotherapy[17] (Level IV; Grade A). In the EXPeRT series, the 5-year EFS in patients with complete (R0) primary or delayed resection was 75.0% in comparison to 28.6% in those who never underwent complete tumor resection.[6]

The feasibility of complete resection of PBL depends on the tumor location, size, and local extension. Though challenging, pancreatic surgical techniques are well established with acceptable morbidity in carefully selected cohorts. As the tumor is often located in the ventral part of the pancreatic head and well encapsulated without connection to the ductal system, a complete local resection is often feasible by performing a pancreaticoduodenectomy.[12] In tumors located in body and tail of the pancreas, a distal pancreatectomy with or without splenectomy is usually performed (Level IV; Grade B). As vascularization of the upper portion of spleen comes from the short gastric vessels, this portion can often be spared, even in the case of infiltration or encasing of the main splenic vessels, avoiding unnecessary and potentially harmful dissection on these structures, which may lead to an increased risk of R1 resection and recurrence. Spleen preservation is particularly important in young children (Level V; Grade B). However, if anyhow possible and prior to attempted distal pancreatectomy, the child should be vaccinated against encapsulated bacteria as recommended by Lee.[45]

Pancreatic insufficiency and relapses seem more frequently described after a pylorus-sparing pancreatoduodenectomy (Traverso-Longmire) than with a classic Whipple surgery (14.3% vs. 5.7%).[9] The latter has been reported to be highly effective and not associated with higher incidence of major complications, when performed in experienced centers[46] (Level IV; Grade B). However, the decision regarding which operation to perform must be left to the treating surgeons after a careful review of the radiological and intraoperative findings. A word of caution must be rendered at this point on minimally invasive surgical (MIS) approaches to the pancreas as robust and vetted data on the use of MIS (either traditional laparoscopy or robotic-assisted surgery)

are lacking. Therefore, MIS approaches cannot be uniformly recommended for all patients in all centers, and they should be reserved for highly selected patients (older age, tumors of the tail) and in expert centers well versed in MIS techniques in the field of oncology (Level V; Grade D).

If a microscopically complete resection (R0) does not seem feasible at diagnosis, patients should be elected for a neoadjuvant chemotherapy. A microscopically incomplete (R1) surgery, or primary debulking and leaving behind gross tumor (R2) is not recommended at diagnosis. Neoadjuvant chemotherapy should be used in unresectable cases of PBL to achieve downstaging of tumors, allowing for complete delayed surgery[4,6,34,47] (Level IV; Grade B). A microscopically incomplete (R1) surgery is an acceptable option only after neoadjuvant treatment, especially in case of close vascular margins. Notably, the preoperative imaging will often allow for detailed assessment of adjacent visceral or vascular involvement. In such cases, the child might be best served if referred to a highly specialized center where more advanced and extensive surgeries (including vascular reconstruction, partial gastrectomy, adrenalectomy, or total splenectomy) can be undertaken to achieve a complete resection (R0) to allow for the best chance of cure. The EXPeRT series confirmed that most patients who were in first complete remission at the time of the analysis had undergone complete resection, either primary or delayed.[6]

In metastatic PBL, an aggressive surgical approach to resect or treat metastatic foci (i.e., liver or lung metastases) is recommended, if feasible after four to six courses of neoadjuvant chemotherapy with resulting local and metastatic tumor control[34,48,49] (Level V; Grade C). Delayed surgery techniques are not different from those performed for immediate primary resection.

The prognosis is worse in patients with involved lymph nodes (N1) present at diagnosis or remaining after tumor resection.[12] The best approach for enlarged lymph nodes with or without PET-CT avidity and with or without response to chemotherapy is still a matter of debate and must be discussed individually with a multidisciplinary team (Level V; Grade C). However, although there are no sufficient data on the need and the extent of lymphadenectomy in PBL (Level V; Grade C), any lymph node found to be suspicious at the preoperative imaging or intraoperatively should be removed at the time of upfront resection for histologic analysis. Enlarged lymph nodes not responding to chemotherapy or showing persistent PET-CT positivity should also be resected at the time of delayed surgery (Level V; Grade C). In the case of lymph node regression after chemotherapy, a sampling of the peripancreatic nodes is proposed (Level V; Grade C). In this setting, an intraoperative frozen-section histopathological analysis can be performed, and if occult disease is found, a formal lymphadenectomy could be proposed (Level V; Grade C).

2.4.2 | Chemotherapy

PBL is considered a chemo-sensitive tumor; however, a standard regimen is yet to be defined[1,3,4,6,49,50] (Level IV; Grade C). In general, neoadjuvant chemotherapy is used in cases of locally advanced, nodal extension, unresectable, metastatic or recurrent tumors. Since PBL generally affects very young children, specific attention to organ toxicities (particularly compromising the function of heart, kidneys, and hearing) is mandatory, and doses of chemotherapy must be adapted accordingly (Level IV; Grade B). The role of adjuvant chemotherapy is unclear in case of initial surgery of PBL (Level IV; Grade C). It was mostly used either after microscopically incomplete (R1) or complete resections (R0) to decrease the risk of tumor relapse and dissemination. The appropriate number of cycles remains to be defined. The total amount of chemotherapy may depend on the number of cycles of neoadjuvant chemotherapy, its efficacy, and maximum cumulative dose of cytotoxic drugs in very young children.

The general scheme and details of chemotherapy of PBL are depicted in Supporting Material S1 and Figure 1.

1. The first-line chemotherapy in children with PBL could be PLADO (cisplatin and doxorubicin) regimen, classically used for hepatoblastoma[51–53] (Level IV; Grade B). The efficacy has been confirmed in the EXPeRT series, where 73% of patients with initially unresectable PBL had a tumor response to primary PLADO chemotherapy.[6]
2. A maximum of six cycles of PLADO is generally recommended (Level IV; Grade B).
3. In patients after initial complete tumor resection (R0), two courses of adjuvant PLADO are recommended; however, in selected cases of very small tumors no adjuvant chemotherapy after R0 resection is an acceptable option (Level IV; Grade C).
4. In patients with initial microscopically incomplete resection (R1), including cases with involved but resected lymph nodes (R1, N1), four courses of adjuvant PLADO are recommended (Level IV; Grade C).
5. In patients with initially unresectable tumors, involved lymph nodes or metastatic disease, a maximum of six courses of PLADO chemotherapy are recommended to achieve PBL downstaging and enable complete delayed surgery (Level IV; Grade B).
6. The tumor response should be assessed after each two courses of chemotherapy to consider tumor resectability (Level V; Grade A).
7. Response to neoadjuvant chemotherapy should be evaluated by MRI or CT according to either World Health Organization (WHO) criteria using bidimensional measurements or RECIST (Response Evaluation Criteria in Solid Tumours) 1.1 using unidimensional measurements[54] (Level IV; Grade C). Due to high resolution and lack of radiation exposure, MRI is particularly recommended in children with PBL.
8. As the decline or normalization of initially elevated serum AFP levels may reflect chemotherapy efficacy, AFP should be monitored closely and the decline compared to its physiological half-life of 6 days[6,15,51] (Level V; Grade B).
9. Complete delayed resection is crucial for initially inoperable PBL:
   a. In case of complete delayed tumor resection (R0) performed after six courses of neoadjuvant PLADO, no adjuvant therapy is recommended.

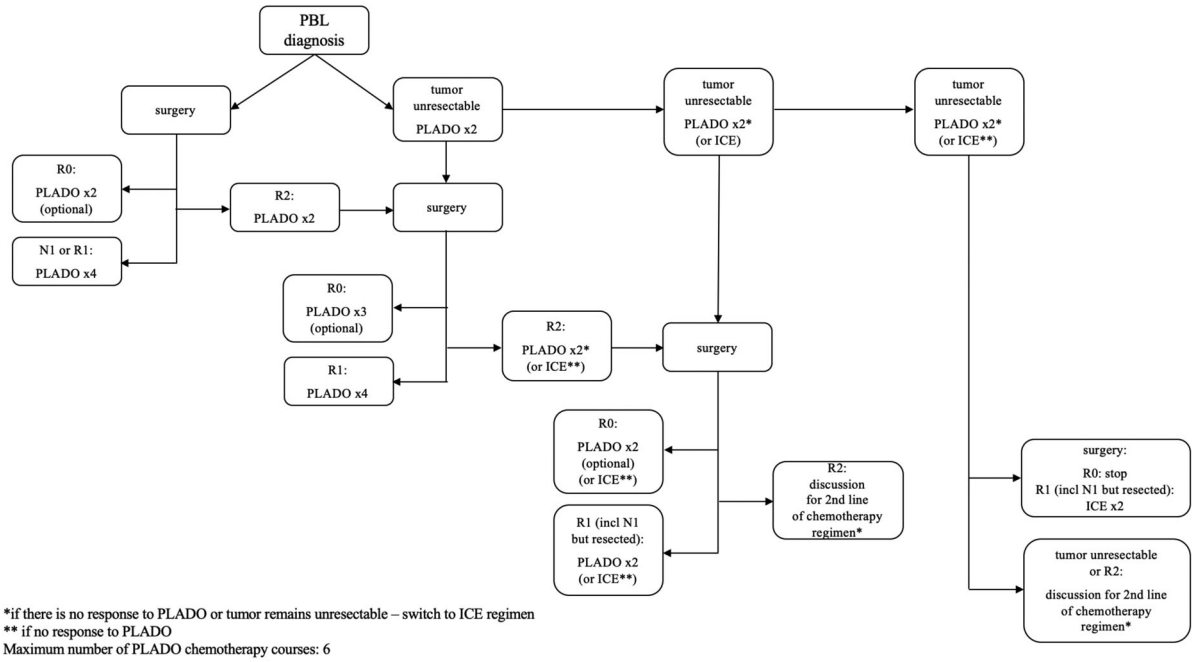

FIGURE 1 Proposal strategy from EXPeRT for the treatment of pediatric pancreatoblastoma. Abbreviations: ICE, ifosfamide carboplatin and etoposide; N1, involved lymph nodes; PLADO, platinum + doxorubicin chemotherapy; R0, complete excision; R1, microscopic residues; R2, macroscopic residues

b. In case of microscopically incomplete delayed surgery (R1) despite neoadjuvant chemotherapy, two postoperative courses of chemotherapy with ICE (ifosfamide, carboplatin, and etoposide) regimen should be administered (Figure 1) (Level IV; Grade B).
c. In case of macroscopically incomplete delayed surgery or still inoperable PBL, the chemotherapy regimen should be switched to ICE or, when impossible or contraindicated, to another chemotherapy regimen (see 10. and 11.)

10. If there is no response to neoadjuvant PLADO regimen or if complete tumor resection remains impossible after four to six courses (tumor still inoperable or after R2 delayed surgery), the switch to the second-line treatment with ICE regimen is proposed (Level IV; Grade C). Another acceptable option is VAC (vincristine, dactinomycin, and cyclophosphamide) regimen (Level V; Grade C).
11. The use of other chemotherapy regimens, including gemcitabine, 5-fluorouracil, vinblastine, and irinotecan[55,56] may be an option and should be discussed within multidisciplinary team of experts in very rare tumors (VRT) in children.
12. The role of high-dose chemotherapy with autologous peripheral blood stem cell rescue has not been established due to a small number of patients treated with this modality, however, it may be a therapeutic strategy in selected patients with high-risk metastatic PBL (Level V; Grade C).[57–61]

2.4.3 | Radiotherapy

The role of radiotherapy (RT) in children with PBL remains unclear. Some authors proposed to deliver RT after macroscopically incomplete delayed surgery (R2) or after relapse,[4,17,49,62] in case of positive margins (R1), nodal involvement (N1), and/or tumor spillage during surgery (Level V; Grade C). However, children with PBL are often very young, so the potential side effects of RT must be considered before administration (Level V; Grade C).

2.4.4 | Therapy of PBL relapse

The long-term survival is still possible for children with relapsed PBL, particularly in those with recurrences feasible to upfront complete surgical resection or to delayed excision of the tumor and/or metastases performed after chemotherapy.[12]

In PBL recurrence confined to the pancreas or regional lymph nodes, an aggressive surgical approach might be recommended as an upfront procedure, if feasible (Level V; Grade C). The location of relapse plays a critical role. Particular care must be undertaken in the case of relapse developing in proximal pancreas in the setting of a patient with a prior pancreaticoduodenectomy as opposed to a child where the relapse is in the tail or body of pancreas following prior distal pancreatectomy. In these cases, surgery alone is likely to be the only treatment and/or curative modality.

In the setting of both local and distant relapses of PBL, the role of surgery becomes less clear except in situation of obstruction, perforation, or hemorrhage. Otherwise, chemotherapy regimen should be initiated to enable delayed resection.[6] Cumulative dosage of the first-line chemotherapy should be considered to define the optimal and less toxic regimen for the treatment of relapse. If feasible, patients may be treated with PLADO regimen. Cardiac, renal, and audiometry evaluations are mandatory in children that had previously been treated with PLADO chemotherapy (Level V; Grade B). In children with PBL relapse who received six cycles of PLADO chemotherapy in the first-line treatment, ICE, VAC, or other regimens with or without anthracyclines might be therapeutic options.[63] The role of high-dose chemotherapy with autologous peripheral blood stem cell rescue, RT and liver transplantation has not been established due to small number of patients treated with these modalities; however, these may be therapeutic strategies in selected cases (Level V; Grade C).[61,64]

2.5 | Follow-up

Long-term follow-up is highly recommended due to the risk of recurrence. There are no established protocols for follow-up after treatment for PBL. It should comprise detailed medical history, physical examination, and imaging studies (abdominal US and MRI or CT) in stages 2 and 3 according to the classification proposed by the EXPeRT group (Table 3), repeated every 3 months in the first and second year after therapy, every 4 months in the third year, every 6 months in the fourth year, and every 12 months thereafter (Level IV; Grade C). Regular monitoring of serum AFP levels may help to detect early recurrence of PBL, particularly in patients with initially elevated levels (Level IV; Grade B). Systematic evaluation of endocrine and exocrine pancreatic functions as well as hearing, cardiac, and renal functions after PLADO chemotherapy, is mandatory (Level IV; Grade B).

2.6 | Screening and prevention recommendations

Genetic counseling should be proposed to all patients with PBL and their families (Level V; Grade B).

Children with genetic syndromes, which predispose to early-onset cancers including PBL, should be screened regularly from early childhood for the development of other embryonal tumors (Beckwith–Wiedemann syndrome) or gastrointestinal tumors (FAP) (Level V; Grade B).

Molecular testing is essential to plan and guide patient care, as tumor risk is stratified among the molecular subtypes of these genetic syndromes.

3 | CONCLUSION

PBL is a VRT that occurs generally in very young children. Treatment and prognosis rely on the feasibility to perform complete surgery and on the response to chemotherapy. Prognosis in children with completely resected PBL is generally good. Some open questions remain including the risk of tumor spillage in the case of initial transperitoneal biopsy, the role of adjuvant chemotherapy, the optimal number of chemotherapy courses, and the role of RT. International collaborative studies with standardized treatment and prospective enrollment in national or international databases are mandatory to improve the knowledge and the prognosis of children with PBL.

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CONFLICT OF INTEREST

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REFERENCES

1. Chung EM, Travis MD, Conran RM. Pancreatic tumors in children: radiologic-pathologic correlation. *Radiographics*. 2006;26(4):1211-1238.

2. Shorter NA, Glick RD, Klimstra DS, Brennan MF, Laquaglia MP. Malignant pancreatic tumors in childhood and adolescence: the Memorial Sloan-Kettering experience, 1967 to present. *J Pediatr Surg*. 2002;37(6):887-892.
3. Klimstra DS, Wenig BM, Adair BM, Heffess CS. Pancreatoblastoma a clinicopathological study and review of the literature. *Am J Surg Pathol*. 1995;19(12):1371-1389.
4. Defachelles AS, De Lassalle EM, Boutard P, Nelken B, Schneider P, Patte C. Pancreatoblastoma in childhood: clinical course and therapeutic management of seven patients. *Med Pediatr Oncol*. 2001;37(1):47-52.
5. Mylonas KS, Nasioudis D, Tsilimigras DI, Doulamis IP, Masiakos PT, Kelleher CM. A population-based analysis of a rare oncologic entity: malignant pancreatic tumors in children. *J Pediatr Surg*. 2018;53(4):647-652.
6. Bien E, Godzinski J, Dall'Igna P, et al. Pancreatoblastoma: a report from the European cooperative study group for paediatric rare tumours (EXPeRT). *Eur J Cancer*. 2011;47:2347-2352.
7. Chisholm KM, Hsu CH, Kim MJJ, Rangaswami A, Gray Hazardt FK. Congenital pancreatoblastoma: report of an atypical case and review of the literature. *J Pediatr Hematol Oncol*. 2012;34(4):310-315.
8. Isobe T, Seki M, Yoshida K, et al. Integrated molecular characterization of the lethal pediatric cancer pancreatoblastoma. *Cancer Res*. 2018;78(4):865-876.
9. Mylonas KS, Doulamis IP, Tsilimigras DI, et al. Solid pseudopapillary and malignant pancreatic tumors in childhood: a systematic review and evidence quality assessment. *Pediatr Blood Cancer*. 2018;65(10):e27114.
10. Nasher O, Hall NJ, Sebire NJ, de Coppi P, Pierro A. Pancreatic tumours in children: diagnosis, treatment and outcome. *Pediatr Surg Int*. 2015;31(9):831-835.
11. Dall'Igna P, Cecchetto G, Bisogno G, et al. Pancreatic tumors in children and adolescents: the Italian TREP project experience. *Pediatr Blood Cancer*. 2010;54(5):675-680.
12. Dhebri AR, Conner S, Campbell F, Ghaneh P, Sutton R, Neoptolemos JP. Diagnosis, treatment and outcome of pancreatoblastoma. *Pancreatology*. 2004;4(5):441-453.
13. Glick RD, Pashankar FD, Pappo A, Laquaglia MP. Management of pancreatoblastoma in children and young adults. *J Pediatr Hematol Oncol*. 2012;34(2):S47-S50.
14. Pancreatoblastoma. https://www.orpha.net/consor/cgi-bin/Disease_Search.php?lng=EN&data_id=844&Disease_Disease_Search_diseaseGroup=pancreatoblastoma&Disease_Disease_Search_diseaseType=Pat&Disease(s)/group%20of%20diseases=Pancreatoblastoma&title=Pancreatoblastoma&search=Disease_Search_Simple. Accessed January 24, 2021.
15. Schneider DT, Calaminus G, Göbel U. Diagnostic value of alpha 1-fetoprotein and beta-human chorionic gonadotropin in infancy and childhood. *Pediatr Hematol Oncol*. 2001;18(1):11-26.
16. Bellizzi AM, Stelow EB. Pancreatic cytopathology: a practical approach and review. *Arch Pathol Lab Med*. 2009;133(3):388-404.
17. Ellerkamp V, Warmann S, Vorwerk P, Leuschner I, Fuchs I. Exocrine pancreatic tumors in childhood in Germany. *Pediatr Blood Cancer*. 2012;58(3):366-371.
18. Bassarova A, Sedloev T, Dimitrova V, Hristova S. Pancreatoblastoma in an adult patient with late recurrence. *J Cytol Histol*. 2015;6:338.
19. Berger KA, Mughal SS, Allgäuer M, et al. Metastatic adult pancreatoblastoma: multimodal treatment and molecular characterization of a very rare disease. *Pancreatology*. 2020;20(3):425-432.
20. Cavallin A, Falconi M, Bortesi L, Crippa S, Barugola G, Butturini G. Pancreatoblastoma in adults: a review of the literature. *Pancreatology*. 2009;9(1-2):73-80.
21. Charlton-Ouw KM, Kaiser CL, Tong GX, Tong GX, Allendorf JD, Chabot JA. Revisiting metastatic adult pancreatoblastoma. A case and review of the literature. *JOP*. 2008;9(6):733-738.
22. Hammer ST, Owens SR. Pancreatoblastoma: a rare, adult pancreatic tumor with many faces. *Arch Pathol Lab Med*. 2013;137(9):1224-1226.
23. Vilaverde F, Reis A, Rodrigues P, Carvalho A, Scigliano H. Adult pancreatoblastoma - case report and review of literature. *J Radiol Case Rep*. 2016;10(8):28-38.
24. Zouros E, Manatakis DK, Delis SG, Agalianos C, Triantopoulou C, Dervenis C. Adult pancreatoblastoma: a case report and review of the literature. *Oncol Lett*. 2015;9(5):2293-2298.
25. Dykewicz CA, Centers for Disease Control and Prevention (U.S.), Infectious Diseases Society of America, American Society of Blood and Marrow Transplantation. Summary of the guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. *Clin Infect Dis*. 2001;33(2):139-144.
26. Orbach D, Ferrari A, Schneider DT, et al. The European Paediatric Rare Tumours Network - European Registry (PARTNER) project for very rare tumors in children. *Pediatr Blood Cancer*. 2021:e29072. https://doi.org/10.1002/pbc.29072
27. Rebhandl W, Felberbauer FX, Puig S, et al. Solid-pseudopapillary tumor of the pancreas (Frantz tumor) in children: report of four cases and review of the literature. *J Surg Oncol*. 2001;76(4):289-296.
28. Shet NS, Cole BL, Iyer RS. Imaging of pediatric pancreatic neoplasms with radiologic-histopathologic correlation. *Am J Roentgenol*. 2014;202(6):1337-1348.
29. Montemarano H, Lonergan GJ, Bulas DI, Selby DM. Pancreatoblastoma: imaging findings in 10 patients and review of the literature. *Radiology*. 2000;214(2):476-482.
30. Schooler GR, Squires JH, Alazraki A, et al. Pediatric hepatoblastoma, hepatocellular carcinoma, and other hepatic neoplasms: consensus imaging recommendations from American College of Radiology Pediatric Liver Reporting and Data System (LI-RADS) Working Group. *Radiology*. 2020;296(3):493-497.
31. Bohl CE, Federico SM, Robinson GW, Bahrami A, Shulkin BL. FDG-PET CT in the evaluation of primary and secondary pancreatic malignancies. *Pediatr Blood Cancer*. 2018;65:e27115.
32. Corrias G, Ragucci M, Basturk O, Saba L, Mannelli L. Pancreatoblastoma with metastatic retroperitoneal lymph node and PET/CT. *Clin Nucl Med*. 2017;42(11):e482-e483.
33. Blohm ME, Vesterling-Hörner D, Calaminus G, Göbel U. Alpha 1-fetoprotein (AFP) reference values in infants up to 2 years of age. *Pediatr Hematol Oncol*. 1998;15(2):135-142.
34. Belletrutti M, Bigam D, Bhargava R, Grundy P. Use of gemcitabine with multi-stage surgical resection as successful second-line treatment of metastatic pancreatoblastoma. *J Pediatr Hematol Oncol*. 2013;35(1):e7-e10.
35. Bergstaesser E, Ohnacker H, Stamm B, Angst R, Imbach P, Gnehm HE. Pancreatoblastoma in childhood: the role of alpha fetoprotein. *Med Pediatr Oncol*. 1998;30:126-127.
36. Rajpal S, Warren RS, Alexander M, et al. Pancreatoblastoma in an adult: case report and review of the literature. *J Gastrointest Surg*. 2006;10(6):829-836.
37. *American Joint Committee on Cancer (AJCC) TNM Staging System*. September 6, 2013. American Cancer Society; April 5, 2016. http://www.cancer.org/cancer/pancreaticcancer/detailedguide/pancreatic-cancer-staging. Accessed January 4, 2017.
38. Metzelder ML, Kuebler JF, Shimotakahara A, Glueer S, Grigull L, Ure BM. Role of diagnostic and ablative minimally invasive surgery for pediatric malignancies. *Cancer*. 2007;109(11):2343-2348.
39. Kerr NJ, Chun YH, Yun K, Heathcott RW, Reeve AE, Sullivan MJ. Pancreatoblastoma is associated with chromosome 11p loss of heterozygosity and IGF2 overexpression. *Med Pediatr Oncol*. 2002;39(1):52-54.
40. Hua C, Shu XK, Lei C. Pancreatoblastoma: a histochemical and immunohistochemical analysis. *J Clin Pathol*. 1996;49(11):952-954.

41. Gu WZ, Zou CC, Zhao ZY, Liang L, Tan HF. Childhood pancreatoblastoma: clinical features and immunohistochemistry analysis. *Cancer Lett*. 2008;264(1):119-126.
42. Antonello D, Gobbo S, Corbo B, Sipos B, Lemoine NR, Scarpa A. Update on the molecular pathogenesis of pancreatic tumors other than common ductal adenocarcinoma. *Pancreatology*. 2009;9(1-2):25-33.
43. Saif MW. Pancreatoblastoma. *J Pancreas*. 2007;8(1):55-63.
44. Perez EA, Gutierrez JC, Koniaris LG, Neville HL, Thompson WR, Sola JE. Malignant pancreatic tumors: incidence and outcome in 58 pediatric patients. *J Pediatr Surg*. 2009;44(1):197-203.
45. Lee GM. Preventing infections in children and adults with asplenia. *Hematology Am Soc Hematol Educ Program*. 2020;2020(1):328-335.
46. Vasudevan SA, Ha TN, Zhu H, et al. Pancreaticoduodenectomy for the treatment of pancreatic neoplasms in children: a Pediatric Surgical Oncology Research Collaborative study. *Pediatr Blood Cancer*. 2020;67(9):e28425.
47. Ghaffarian AA, Book L, Meyers RL. Liver transplant for metastatic pancreatoblastoma: 7-year event-free survival after chemotherapy, pancreatectomy, complete hepatectomy, and liver transplant. *Pediatr Transplant*. 2018;22(1). https://doi.org/10.1111/petr.13098
48. Grosfeld JL, Vane DW, Rescorla FJ, McGuire W, West KW. Pancreatic tumors in childhood: analysis of 13 cases. *J Pediatr Surg*. 1990;25(10):1057-1062.
49. Murakami T, Ueki K, Kawakami H, et al. Pancreatoblastoma: case report and review of treatment in the literature. *Med Pediatr Oncol*. 1996;27(3):193-197.
50. Chun Y, Kim W, Park K, Lee S. Pancreatoblastoma. *J Pediatr Surg*. 1997;32(11):1612-1615.
51. Ogawa T, Okinaga K, Obana K, et al. Pancreatoblastoma treated by delayed operation after effective chemotherapy. *J Pediatr Surg*. 2000;35(11):1663-1665.
52. Perilongo G, Brown J, Shafford E, et al. Hepatoblastoma presenting with lung metastases: treatment results of the first cooperative, prospective study of the International Society of Paediatric Oncology on childhood liver tumors. *Cancer*. 2000;89(8):1845-1853.
53. Morgan ER, Perryman JH, Reynolds M, Gonzalez-Crussi FJ. Pancreatic blastomatous tumor in a child responding to therapy used for hepatoblastoma: case report and review of the literature. *Med Pediatr Oncol*. 1996;26(4):284-292.
54. Tirkes T, Hollar MA, Tann M, Kohli MD, Akisik F, Sandrasegaran K. Response criteria in oncologic imaging: review of traditional and new criteria. *Radiographics*. 2013;33(5):1323-1341.
55. Dhamne C, Herzog CE. Response of relapsed pancreatoblastoma to a combination of vinorelbine and oral cyclophosphamide. *J Pediatr Hematol Oncol*. 2015;37(6):e378-e380.
56. Vannier JP, Flamant F, Hemet J, et al. Pancreatoblastoma: response to chemotherapy. *Med Pediatr Oncol*. 1991;19(3):187-191.
57. Hamidieh AA, Jalili M, Khojasteh O, Ghavamzadeh A. Autologous stem cell transplantation as treatment modality in a patient with relapsed pancreatoblastoma. *Pediatr Blood Cancer*. 2010;55(3):573-576.
58. Meneses CF, Osório CD, de Castro Junior CG, Brunetto AL. Autologous stem cell transplantation as first line treatment after incomplete excision of pancreatoblastoma. *Rev Bras Hematol Hemoter*. 2013;35(2):148-149.
59. Souzaki R, Tajiri T, Kinoshita Y, et al. Successful treatment of advanced pancreatoblastoma by a pylorus-preserving pancreatoduodenectomy after radiation and high-dose chemotherapy. *Pediatr Surg Int*. 2010;26(10):1045-1048.
60. Yonekura T, Kosumi T, Hokim M, Hirooka S, Kitayama H, Kubota A. Aggressive surgical and chemotherapeutic treatment of advanced pancreatoblastoma associated with tumor thrombus in portal vein. *J Pediatr Surg*. 2006;41:596-598.
61. Pfrommer S, Weber A, Dutkowski P, et al. Successful salvage chemotherapy with FOLFIRINOX for recurrent mixed acinar cell carcinoma and ductal adenocarcinoma of the pancreas in an adolescent patient. *Case Rep Oncol*. 2013;6:497-503.
62. Vossen S, Goretzki PE, Goebel U, Willnow U. Therapeutic management of rare malignant pancreatic tumors in children. *World J Surg*. 1998;22(8):879-882.
63. Brennan B. Pancreatoblastoma. August 2004. www.orpha.net/data/patho/GB/uk-pancrea.pdf
64. Reggiani G, Affinita MC, Dall'Igna P, Virgone C, Sorbara S, Bisogno G. Treatment strategies for children with relapsed pancreatoblastoma: a literature review. *J Pediatr Hematol Oncol*. 2020. https://doi.org/10.1097/mph.0000000000002033

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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