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MULTIMEDIA ARTICLE - Slide show

Pancreatoblastoma

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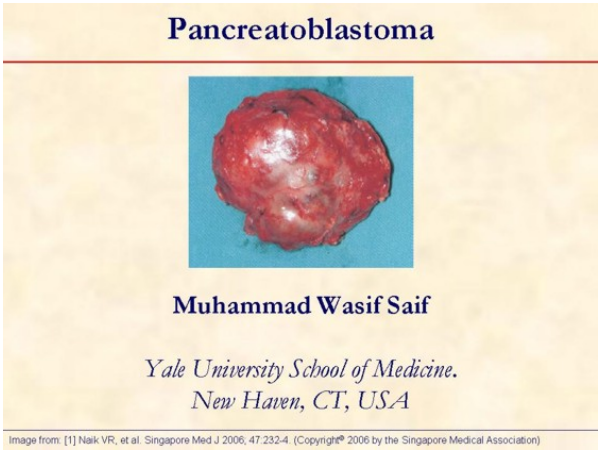
Summary

Pancreatoblastoma (PB), or infantile pancreatic carcinoma, is an extremely rare pancreatic tumor in childhood, comprising 0.5% of pancreatic non-endocrine tumors. Although PB mainly presents during childhood but can also occur in adults. PB tend to be less aggressive in infants and children compared to adults. Children with PB usually present late with upper abdominal pain and many have a palpable mass in the epigastrium. Mechanical obstruction of the upper duodenum and gastric outlet by tumor in the head of the pancreas may be associated with vomiting, jaundice and gastrointestinal bleeding. Histologically, PB is characterized with distinct acinar and squamoid cell differentiation. PB has been associated with alterations in the Wnt signaling pathway and chromosome 11p loss of heterozygosity (LOH), Beckwith-Wiedemann syndrome and familial adenomatous polyposis. The majority of these tumors arise in the head of the pancreas. Alpha-fetoprotein may be elevated in up to 68% of patients with PB. Ultrasound and CT scan may be useful but preoperative diagnosis is often quite difficult. The treatment of choice is complete resection, that may often be curative. The role of adjuvant chemotherapy or radiotherapy is still under discussion due to small number of patients treated as yet. Chemotherapy regimens consisting of cyclophosphamide, etoposide, doxorubicin, and cisplatin have been used in neoadjuvant setting with anecdotal benefit. Prognosis of this rare tumor is good, when resected completely. Prognosis is poorer, when there is metastasis or when it is inoperable. On the whole, PB is regarded to be a curable tumor; hence the clinical diagnosis should be made early. Awareness of this rare tumor of pancreas is essential for early detection and proper management. The author review the clinical presentation, etiology, diagnosis, treatment and prognosis of PB in this presentation.



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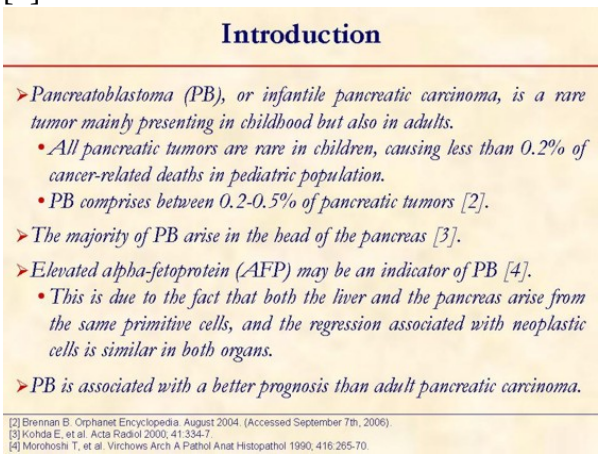
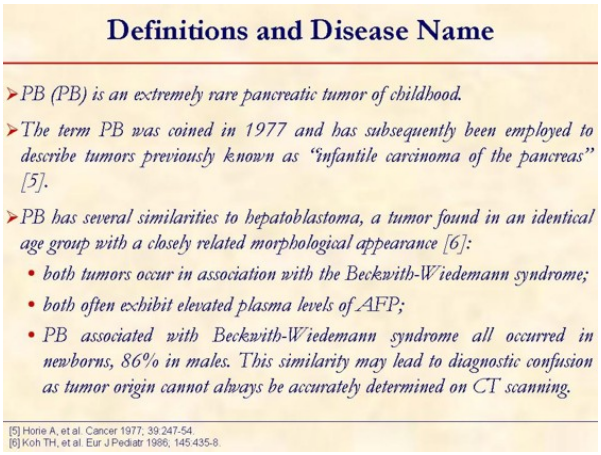
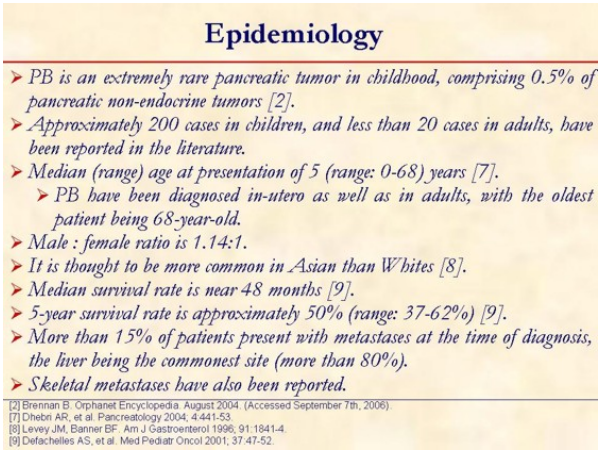


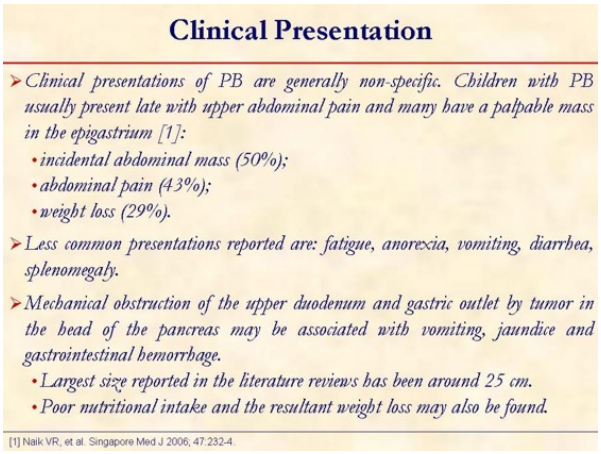
Pancreatoblastoma (PB), is an extremely rare pancreatic tumor of childhood, but can occur in adults. PB often exhibits elevated plasma levels of alpha-fetoprotein. PB, though not common, is said to be less aggressive in infants and children compared to adults [2, 3, 4].



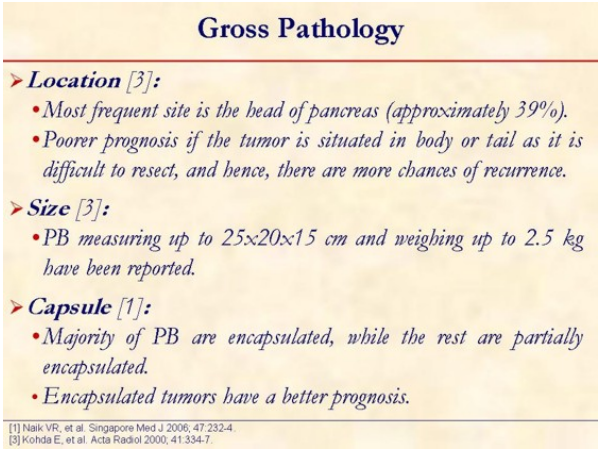
PB is an extremely rare pancreatic tumor of childhood. The term PB was coined by Horie *et al*. in 1977 to describe tumors previously known as "infantile carcinoma of the pancreas" [5]. PB has several similarities to hepatoblastoma, including association with the Beckwith-Wiedemann syndrome and elevated plasma levels of alpha-fetoprotein (AFP) [6].



Pancreatic tumors are rare in children, and PB comprises only 0.5% of pancreatic non-endocrine tumors occurring in children. This tumor is more common in Asians than in the white population. They have also been diagnosed in-utero and in adults, with the oldest patient being 68-year-old. [2, 7, 8, 9]

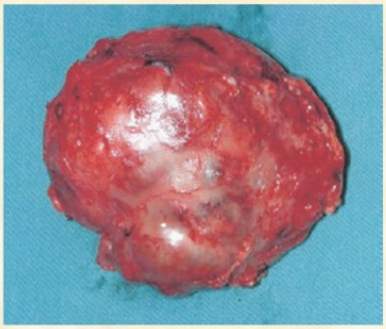


The presenting complaints are varied (for instance we observed a patient who had no prior complaints and was identified following investigations after a motor vehicle accident). Children with PB usually present late with upper abdominal pain and many have a palpable mass in the epigastrium [1]. Mechanical obstruction of the upper duodenum and gastric outlet by tumor in the head of the pancreas can complicate with obstruction and gastrointestinal bleeding. Poor nutritional intake and the resultant weight loss may also be found.



Largest size reported in the literature reviews has been around 15 cm. Majority of the tumors are encapsulated, while the rest are partially encapsulated. Encapsulated tumors have a better prognosis. [1, 3]

Gross Pathology



[1] Naik VR, et al. Singapore Med J 2006; 47:232-4. (Copyright© 2006 by the Singapore Medical Association)

The specimen photograph shows an encapsulated tumor with a nodular surface. The capsule is complete [1].

Etiology

- ***Wnt signaling pathway:*** *alterations in the Wnt signaling pathway and chromosome 11p loss of heterozygosity (LOH) [10].*
- ***Beckwith-Wiedemann syndrome****: molecular association between PB and other embryonal tumors, such as hepatoblastoma and Wilm's tumor, has been previously suggested by the presentation of Beckwith-Wiedemann in children with these tumors [6, 11, 12].*
- ***Familial adenomatous polyposis:*** *has been also associated with PB [13].*

[6] Koh TH, et al. Eur J Pediatr 1986; 145:435-8.
[10] Kerr NJ, et al. Med Pediatr Oncol 2002; 39:52-4.
[11] Drut R, Jones MC. Pediatr Pathol 1988; 8:331-9.
[12] Potts SR, et al. Z Kinderchir 1986; 41:56-7.
[13] Abraham SC, et al. Am J Pathol 2001; 159:1619-27.

Molecular investigation has disclosed a mosaic paternal 11p15 uniparental disomy in the tumor cells of PB. Recently genetic alterations also have been characterized and the commonest change is allelic loss of 11p. Familial adenomatous polyposis and Beckwith-Wiedemann syndrome have also been associated with PB. [6, 10, 11, 12, 13]

Histogenesis

- *Histogenesis of PB is still uncertain [14].*
- *It is believed to be hamartomatous or dysembryogenic development of ductal cells of ventral portion of primordial pancreas.*
- *PB contains pluripotent cells capable of differentiating along the pathway of all three pancreatic cell types.*

[14] Klimstra DS, et al. Am J Surg Pathol 1995; 19:1371-89.

It is said to be that hamartomatous or dysembryogenic development of ductal cells of ventral portion of primordial pancreas lead to the development of PB. PB contains pluripotent cells capable of differentiating along the pathway of all three pancreatic cell types: acinar, endocrine and ductal. [14]

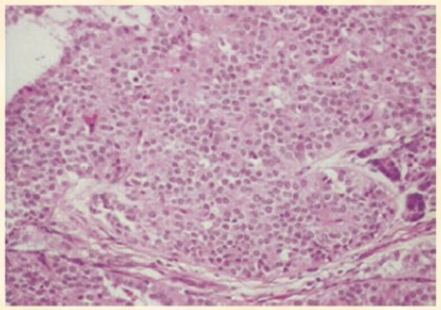
Histology [14,15,16]

- *Histologically, PB exhibits dense cellularity with acinar differentiation and characteristic "squamoid corpuscules". PB has distinct acinar and squamoid cell differentiation.*
- *Both cystic change and calcification have been described within individual tumors.*
- *Most cases are formed of an epithelial component (usually predominant) separated into distinct lobules by fibrous stoma.*
- *The epithelial component usually consists of distinct acini, solid sheets and "squamoid corpuscules".*
- *Eosinophilic cells with zymogen-type granules may be present and there may be teratoid differentiation into cartilage, bone, osteoid or spindle cells.*
- *Squamous, glandular and undifferentiated elements may be intermingled in an organoid fashion.*

[14] Klimstra DS, et al. Am J Surg Pathol 1995; 19:1371-89.
[15] Silverman JF, et al. Acta Cytol 1990; 34:632-40.
[16] Palosaari D, et al. Arch Pathol Lab Med 1986; 110:650-2.

PB can exhibit acinar, endocrine and ductal differentiation. Histopathological features that are readily seen include hemorrhage, capsule formation and necrosis. [14, 15, 16]

Histology



[1] Naik VR, et al. Singapore Med J 2006; 47:232-4. (Copyright© 2006 by the Singapore Medical Association)

Photomicrograph shows a cellular tumor with uniform epithelial cells arranged in nests and acini (hematoxylin and eosin, x250) [1].

Immunohistochemistry [15,16]

- *Immunohistochemistry is usually strongly positive for alpha-1-antitrypsin and glucose-6-phosphatase, in addition acid phosphatase, esterase and enteroprotease activity may be demonstrated using histochemistry.*
- *Stains for chromogranin, synaptophysin and neuron-specific enolase are often positive.*
- *Trypsin and chymotrypsin are usually found in acinar regions but positivity for specific peptide hormones is rare.*
- *Immunohistochemistry for AFP may be positive within solid regions of the epithelial component.*
- *Electron microscopy reveals multiple cytoplasmic neurosecretory zymogen granules.*

[15] Silverman JF, et al. Acta Cytol 1990; 34:632-40.
[16] Palosaari D, et al. Arch Pathol Lab Med 1986; 110:650-2.

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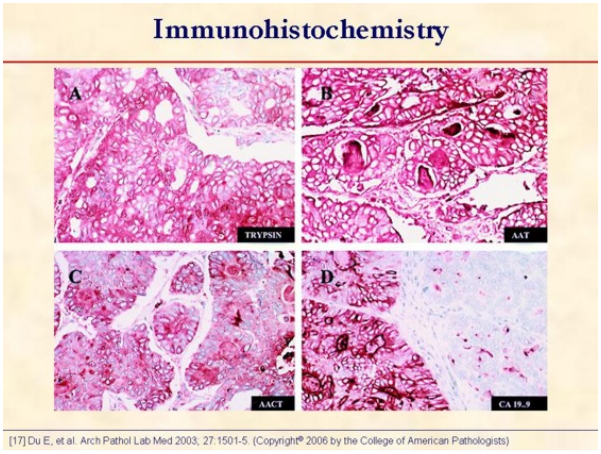
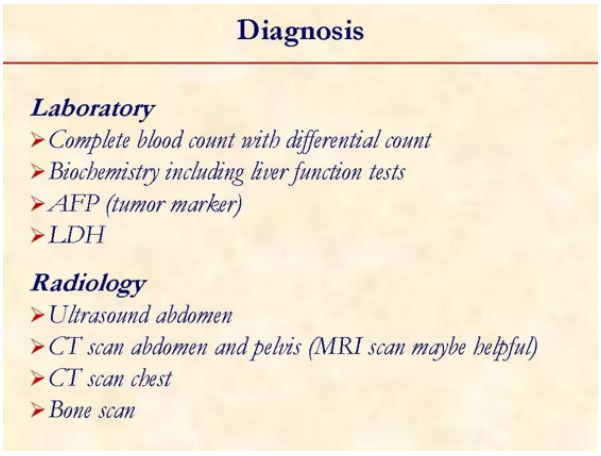
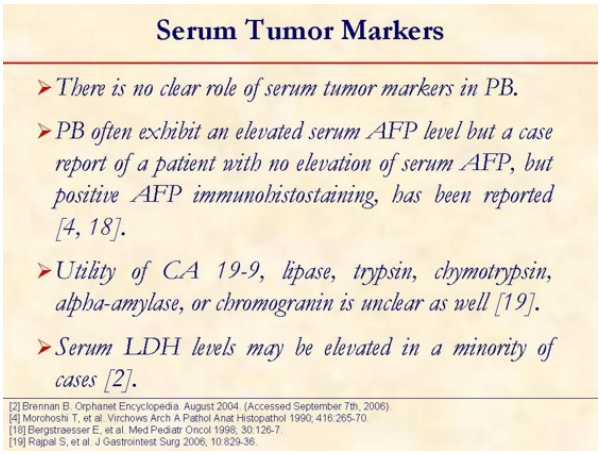


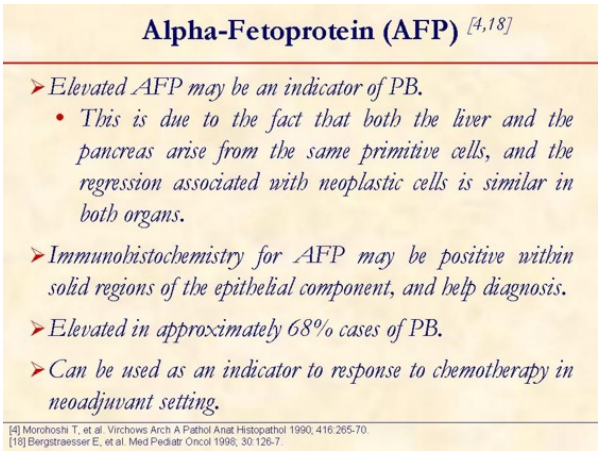
The tumor cells show strong positive immune reaction for trypsin (A), alpha1-antitrypsin (B), alpha1-antichymotrypsin (C), and CA 19-9 (D). Note that the luminal contents are positive for alpha1-antitrypsin (B), alpha1-antichymotrypsin (C), and CA 19-9 (D) (original magnifications x400) [17].



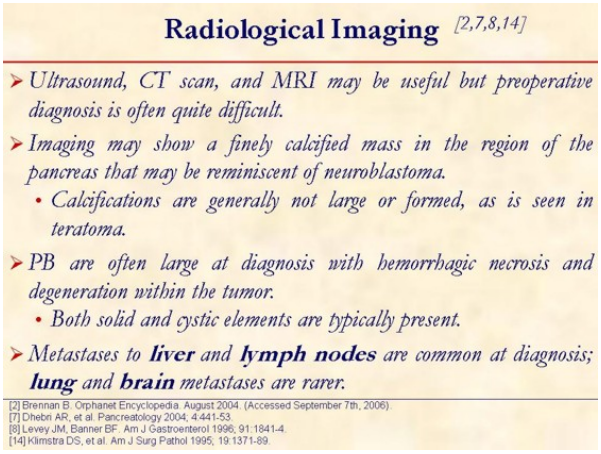
Biochemistry and radiology are the main diagnostic tools in PB.



AFP is the most commonly used tumor marker in PB. Other tumor markers do not show any significant correlation. [2, 4, 18, 19]

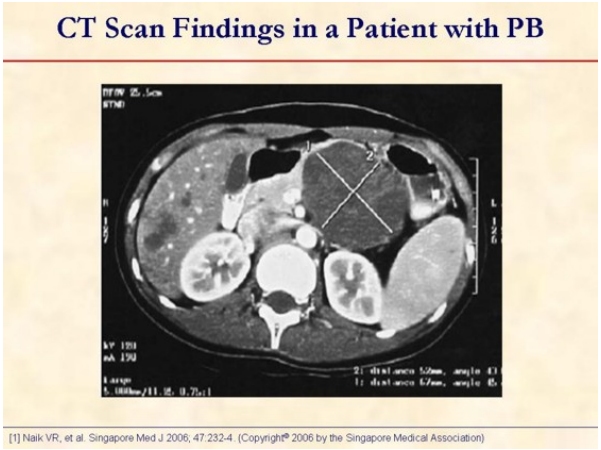


Elevated serum AFP levels have been reported in up 68% of cases. AFP level comes down once the tumor is resected. [4, 18]



Radiological staging include a CT scan of abdomen, pelvis and chest. Bone scan or a brain MRI may be performed if clinically indicated. [2, 7, 8, 14]

CT Scan Findings in a Patient with PB



[1] Naik VR, et al. Singapore Med J 2006; 47:232-4. (Copyright© 2006 by the Singapore Medical Association)

Enhanced axial CT image shows a large well-defined cystic tumor in the tail of pancreas and multiple small nodules in the liver [1].

Differential Diagnosis (1)

- *The most common cystic pancreatic neoplasms in children are microcystic adenomas and cystadenocarcinomas.*
- *Their appearance is similar to that in adults.*
- *They may cause a pseudomyxoma peritonei if they rupture into the peritoneum.*

The most common cystic pancreatic tumors in children are microcystic adenomas and cystadenocarcinomas.

Differential Diagnosis (2)

Pancreatic tumors in children are classified as epithelial (non-endocrine and endocrine) and non-epithelial in origin

Non-epithelial tumors	Epithelial (non-endocrine and endocrine)
Non-epithelial tumors: *primary lymphoma, primitive neuroectodermal tumor (PNET) and sarcoma, or metastases; lymphoma is the most common type.*	***Malignant non-endocrine:*** *PB and papillary carcinoma.*
Benign non-endocrine: *adenomas and dermoid cysts (teratoma).*	***Endocrine:*** *nesidioblastosis and insulinoma.*
	Most common cystic pancreatic neoplasms: *microcystic adenomas and cystadenocarcinomas. Their appearance is similar to that in adults. They may cause a pseudomyxoma peritonei if they rupture into the peritoneum.*

Differentiation of PB from other tumors is extremely important as prognosis of this rare tumor is good, when resected completely.

Differential Diagnosis (3)

Clinically PB can be distinguished from the following neuroendocrine tumors due to their different spectrum of symptoms:

Disease	Features
Insulinoma	*Hypoglycemia, behavior change, weight gain and/or morning seizures*
Gastrinoma	*Severe gastrointestinal ulceration and diarrhea*
VIPoma	*Watery diarrhea, hyperkalemic and achlorhydia*
Glucagonomas	*Migratory necrolytic dermatitis, weight loss, stomatitis, anemia and hyperglycemia*
Somatostatinomas	*Diarrhea and may develop diabetes mellitus*

Clinically PB can be distinguished from the following neuroendocrine tumors due to their different spectrum of symptoms. Insulinoma: hypoglycemia, behavior change, weight gain and/or morning seizures; Gastronoma: severe gastrointestinal ulceration and diarrhea; VIPoma: watery diarrhea, hyperkalemic and achlorhydia; Glucagonomas: migratory necrolytic dermatitis, weight loss, stomatitis, anemia and hyperglycemia; Somatostatinomas: diarrhea and may develop diabetes mellitus.

Staging [20]

- *The tumor, node, metastasis (TNM) classification of the American Joint Committee on Cancer is usually used to determine the tumor staging.*

[20] American Joint Committee on Cancer: AJCC Cancer Staging Manual. 6th ed.

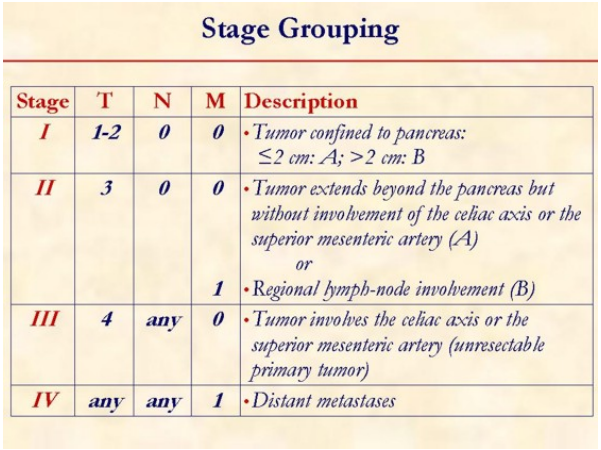
TNM Staging

TNM definitions

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 in greatest dimension*
- *T2: Tumor limited to the pancreas, >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*

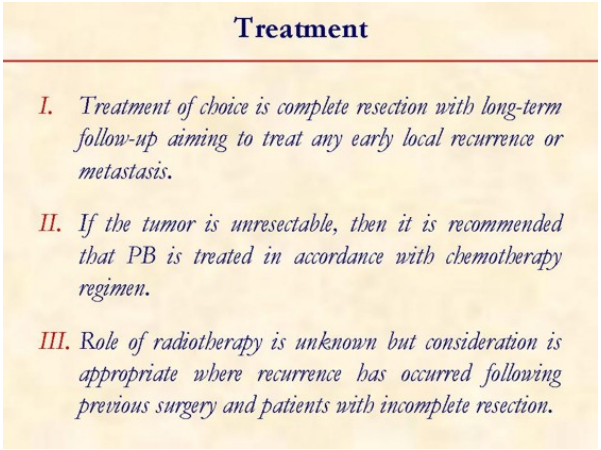
Distant metastasis (M)
- *MX: Distant metastasis cannot be assessed*
- *M0: No distant metastasis*
- *M1: Distant metastasis*



Stage Grouping

Stage	T	N	M	Description
I	1-2	0	0	• Tumor confined to pancreas: ≤2 cm: A; >2 cm: B
II	3	0	0	• Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery (A)
				or
			1	• Regional lymph-node involvement (B)
III	4	any	0	• Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)
IV	any	any	1	• Distant metastases

The tumor, node, metastasis (TNM) classification of the American Joint Committee on Cancer is usually used to determine the tumor staging [20].



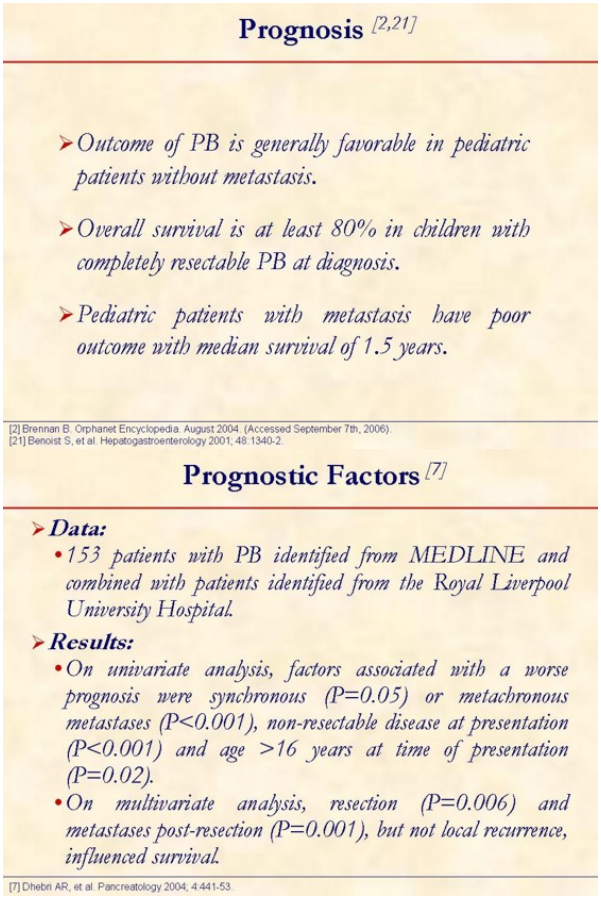
Treatment

I. Treatment of choice is complete resection with long-term follow-up aiming to treat any early local recurrence or metastasis.

II. If the tumor is unresectable, then it is recommended that PB is treated in accordance with chemotherapy regimen.

III. Role of radiotherapy is unknown but consideration is appropriate where recurrence has occurred following previous surgery and patients with incomplete resection.

PB has an indolent course and is amenable for various modes of treatment but surgery is the most optimal treatment.



Prognosis [2,21]

- Outcome of PB is generally favorable in pediatric patients without metastasis.
- Overall survival is at least 80% in children with completely resectable PB at diagnosis.
- Pediatric patients with metastasis have poor outcome with median survival of 1.5 years.

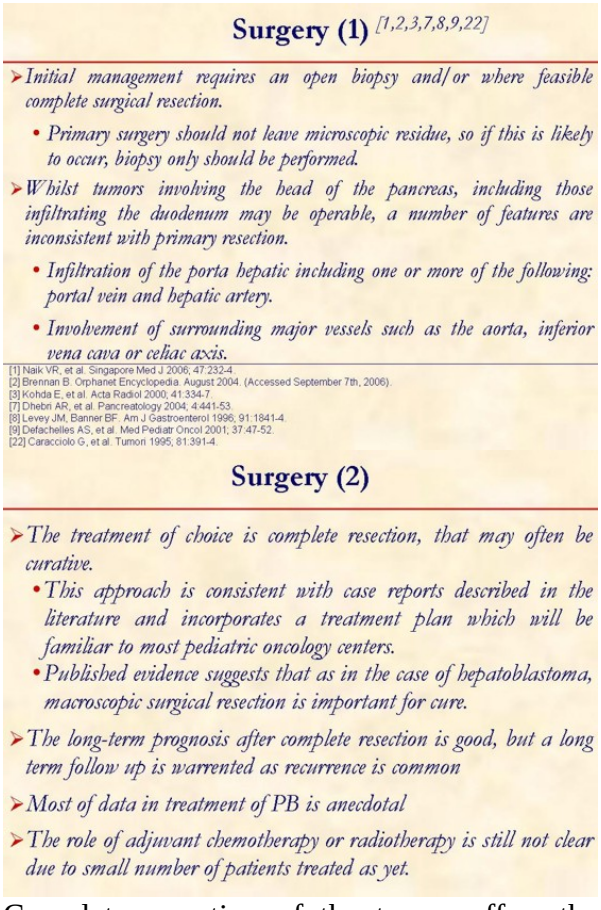
[2] Brennan B. Orphanet Encyclopedia. August 2004. (Accessed September 7th, 2006).
[21] Benoist S, et al. Hepatogastroenterology 2001; 48:1340-2.

Prognostic Factors [7]

- **Data:**
  - 153 patients with PB identified from MEDLINE and combined with patients identified from the Royal Liverpool University Hospital.
- **Results:**
  - On univariate analysis, factors associated with a worse prognosis were synchronous (P=0.05) or metachronous metastases (P<0.001), non-resectable disease at presentation (P<0.001) and age >16 years at time of presentation (P=0.02).
  - On multivariate analysis, resection (P=0.006) and metastases post-resection (P=0.001), but not local recurrence, influenced survival.

[7] Dhebri AR, et al. Pancreatology 2004; 4:441-53.

PB is less aggressive in infants and children compared to adults. Prognosis of PB is good, when resected completely. Prognosis is poorer, when there is metastasis or when it is inoperable. [2, 7, 21]



Surgery (1) [1,2,3,7,8,9,22]

- Initial management requires an open biopsy and/or where feasible complete surgical resection.
  - Primary surgery should not leave microscopic residue, so if this is likely to occur, biopsy only should be performed.
- Whilst tumors involving the head of the pancreas, including those infiltrating the duodenum may be operable, a number of features are inconsistent with primary resection.
  - Infiltration of the porta hepatic including one or more of the following: portal vein and hepatic artery.
  - Involvement of surrounding major vessels such as the aorta, inferior vena cava or celiac axis.

[1] Naik VR, et al. Singapore Med J 2006; 47:232-4.
[2] Brennan B. Orphanet Encyclopedia. August 2004. (Accessed September 7th, 2006).
[3] Kohda E, et al. Acta Radiol 2000; 41:334-7.
[7] Dhebri AR, et al. Pancreatology 2004; 4:441-53.
[8] Levey JM, Banner BF. Am J Gastroenterol 1996; 91:1841-4.
[9] Defachelles AS, et al. Med Pediatr Oncol 2001; 37:47-52.
[22] Caracciolo G, et al. Tumori 1995; 81:391-4.

Surgery (2)

- The treatment of choice is complete resection, that may often be curative.
  - This approach is consistent with case reports described in the literature and incorporates a treatment plan which will be familiar to most pediatric oncology centers.
  - Published evidence suggests that as in the case of hepatoblastoma, macroscopic surgical resection is important for cure.
- The long-term prognosis after complete resection is good, but a long term follow up is warrented as recurrence is common
- Most of data in treatment of PB is anecdotal
- The role of adjuvant chemotherapy or radiotherapy is still not clear due to small number of patients treated as yet.

Complete resection of the tumor offers the best prognosis. However, in the presence of metastatic disease, it is of limited value. [1, 2, 3, 7, 8, 9, 22]

Chemotherapy [1,2,3,7,8,9,23,24,25]

- In metatstatic and unresectable PB, chemotherapy regimens including cisplatin and doxorubicin have been used.
- Prolonged survival(>3 years) after resection of PB and synchronous liver metastases in an adult with adjuvant chemotherapy was reported.
- Other chemotherapy regimens such as cyclophosphamide, and etoposide have been used in neoadjuvant setting with anecdotal benefit.

[1] Naik VR, et al. Singapore Med J 2006; 47:232-4.
[2] Brennan B. Orphanet Encyclopedia. August 2004. (Accessed September 7th, 2006).
[3] Kohda E, et al. Acta Radiol 2000; 41:334-7.
[7] Dhebri AR, et al. Pancreatology 2004; 4:441-53.
[8] Levey JM, Banner BF. Am J Gastroenterol 1996; 91:1841-4.
[9] Defachelles AS, et al. Med Pediatr Oncol 2001; 37:47-52.
[23] Vannier JP, et al. Med Pediatr Oncol 1991; 19:187-91.
[24] Inomata Y, et al. J Pediatr Surg 1992; 27:1570-2.
[25] Ogawa B, et al. J Pediatr Surg 2000; 35:1663-5.

Chemotherapy Regimen

- Chemotherapy regimens consisting of the following agents have been used to treat PB:
  - Cisplatin
  - Carboplatin
  - Cyclophosphamide
  - Ifosfamide
  - Etoposide
  - Doxorubicin
  - Vincristine

First-Line Chemotherapy [26]

- If the tumor is unresectable, then in view of the many similarities between PB and hepatoblastoma, it is recommended that PB is treated in accordance with SIOPEL, i.e. the **PLADO** chemotherapy arm:
  - Day 1: cisplatinum (PLA) 80 mg/m^2/day in continuous i.v. infusion for 24 hours
  - Day 2: doxorubicin (DO) 30 mg/m^2/day in continuous i.v. infusion for 48 hours, i.e. total of 60 mg/m^2/course.
- Literature suggests administration of a total of six courses of PLADO chemotherapy followed by surgical excision if feasible. AFP can show response to chemotherapy.
- Chemotherapy (**A-1 regimen**) consisting of cyclophosphamide, etoposide, pirarubicin, and cisplatin have been used in neoadjuvant setting with anecdotal benefit.

[26] Perilongo G, et al. Cancer 2000; 89:1845-53.

Second-Line Chemotherapy

- Second line chemotherapy with **ICE**
  - ifosfamide
  - carboplatin
  - etoposide

  may be given if renal function is adequate.
- Otherwise a combination of vincristine, actinomycin D and cyclophosphamide is suggested.
- Other agents include mitomycin-A.

Neoadjuvant Chemotherapy [25]

Study:
- Retrospective review of 7 cases of PB treated in France over a 20-year period
- 5 tumor resections were performed:
  - 1 initially;
  - 4 after neoadjuvant chemotherapy (**cisplatin plus doxorubicin**).
  - 2 children received post-operative radiotherapy (secondary to incomplete resection)

Outcome:
- 4 children are disease free: median follow-up of 50 months (range: 5-120 months):
  - 1 had a complete removal of tumor at diagnosis and no further treatment,
  - 3 had unresectable tumor at diagnosis and received neoadjuvant chemotherapy (1 of them also received post-operative radiotherapy)

Conclusions:
- PB is a curable tumor
- Complete resection is the treatment of choice
- Neoadjuvant chemotherapy may reduce tumor volume in unresectable tumor (often the case)
- In patients with incompletely resected disease, postoperative radiotherapy may be indicated

[25] Ogawa B, et al. J Pediatr Surg 2000; 35:1663-5.

In these situations where there are suspected or documented metastatic lesions, empirical chemotherapy regimens that include cisplatin and doxorubicin have been used. A higher rate of metachronous metastasis has been reported in patients undergoing chemotherapy. [1, 2, 3, 7, 8, 9, 23, 24, 25, 26]

Radiotherapy [27]

- The role of radiotherapy is unknown but consideration is appropriate where recurrence has occurred following previous surgery and chemotherapy.
- Radiotherapy may be indicated for either a persistently unresectable tumor of following grossly incomplete resection or microscopic disease but is usually reserved for relapse.

[27] Griffin BR, et al. Cancer 1987; 60:1734-6.

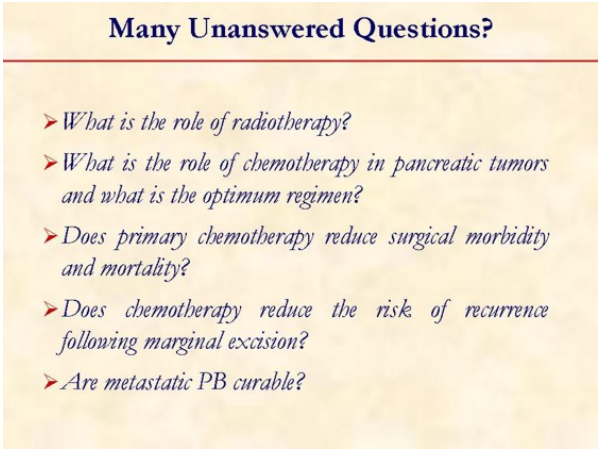
When the tumor is unresectable and the patient is non-responsive to chemotherapy, radiotherapy is given. Shrinkage of PB has been reported after treatment with radiotherapy [27].

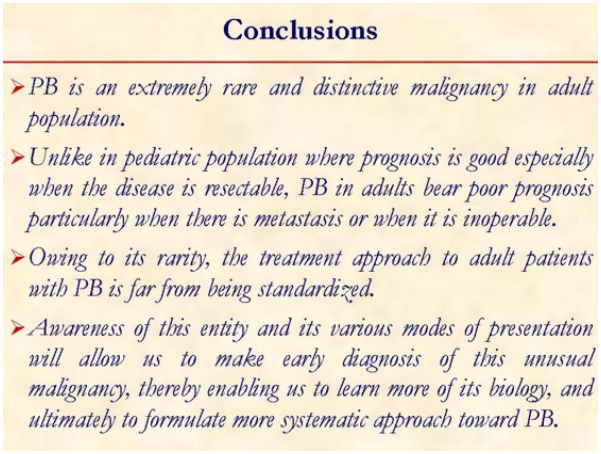
PB in Adults [8,16,17]

- PB is an even rarer entity in adult population.
- Among adult cases that were reported, an age range of 19 to 78 years is reported with male-female ratio of 1:1.3
- PB shows no preferential location adult, but the most frequent site was the head of pancreas (up to 39%) in pediatric cases.
- The prognosis of PB in adult population is poor.
- Adults with PB has a median survival time of approximately 10 months.
- Greater than 50% of adult patients reported died of PB in less than 3 years.

[8] Levey JM, Banner BF. Am J Gastroenterol 1996; 91:1841-4.
[16] Palosaari D, et al. Arch Pathol Lab Med 1986; 110:650-2.
[17] Du E, et al. Arch Pathol Lab Med 2003; 127:1501-5.

[8, 16, 17]





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Abbreviations LOH: loss of heterozygosity; PB: pancreatoblastoma

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