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Contents

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EDITORIAL

- 974 How to identify early complications in patients undergoing distal gastrectomy?
Tropeano G, Chiarello MM, Fico V, Brisinda G
- 982 Quality assessment of surgery for colorectal cancer: Where do we stand?
Morarasu S, Livadaru C, Dimofte GM
- 988 Emerging molecules, tools, technology, and future of surgical knife in gastroenterology
Kumar A, Goyal A
- 999 Carcinoembryonic antigen in the diagnosis, treatment, and follow-up of focal liver lesions
Dilek ON, Arslan Kahraman Dİ, Kahraman G
- 1008 Relationship between *Helicobacter pylori* infection and colorectal polyp/colorectal cancer
Liu Y, Yang DQ, Jiang JN, Jiao Y

MINIREVIEWS

- 1017 Near-infrared cholangiography with intragallbladder indocyanine green injection in minimally invasive cholecystectomy
Symeonidis S, Mantzoros I, Anestiadou E, Ioannidis O, Christidis P, Bitsianis S, Bisbinas V, Zapsalis K, Karastergiou T, Athanasiou D, Apostolidis S, Angelopoulos S
- 1030 Blastomas of the digestive system in adults: A review
Liu Y, El Jabbour T, Somma J, Nakanishi Y, Ligato S, Lee H, Fu ZY

ORIGINAL ARTICLE

Retrospective Study

- 1043 Single-center retrospective study of the diagnostic value of double-balloon enteroscopy in Meckel's diverticulum with bleeding
He T, Yang C, Wang J, Zhong JS, Li AH, Yin YJ, Luo LL, Rao CM, Mao NF, Guo Q, Zuo Z, Zhang W, Wan P
- 1055 Prognostic value of a nomogram model for postoperative liver metastasis of colon cancer
Cheng DX, Xu KD, Liu HB, Liu Y
- 1066 Computer-assisted three-dimensional individualized extreme liver resection for hepatoblastoma in proximity to the major liver vasculature
Xiu WL, Liu J, Zhang JL, Wang JM, Wang XF, Wang FF, Mi J, Hao XW, Xia N, Dong Q
- 1078 Research on the prognostic value of adjusting intraperitoneal three-dimensional quality evaluation mode in laparoscopic cholecystectomy patients
Zhou Y, Chen ZQ

- 1087** Construction of a predictive model for acute liver failure after hepatectomy based on neutrophil-to-lymphocyte ratio and albumin-bilirubin score

Li XP, Bao ZT, Wang L, Zhang CY, Yang W

- 1097** Predicting short-term thromboembolic risk following Roux-en-Y gastric bypass using supervised machine learning

Ali H, Inayat F, Moond V, Chaudhry A, Afzal A, Anjum Z, Tahir H, Anwar MS, Dahiya DS, Afzal MS, Nawaz G, Sohail AH, Aziz M

- 1109** Comparative analysis of two digestive tract reconstruction methods in total laparoscopic radical total gastrectomy

Dong TX, Wang D, Zhao Q, Zhang ZD, Zhao XF, Tan BB, Liu Y, Liu QW, Yang PG, Ding PA, Zheng T, Li Y, Liu ZJ

- 1121** Incidence of surgical site infection in minimally invasive colorectal surgery

Ni LT, Zhao R, Ye YR, Ouyang YM, Chen X

Observational Study

- 1130** Burden of gallstone disease in the United States population: Prepandemic rates and trends

Unalp-Arida A, Ruhl CE

Prospective Study

- 1149** Kuicolong-yu enema decoction retains traditional Chinese medicine enema attenuates inflammatory response ulcerative colitis through TLR4/NF- κ B signaling pathway

Han L, Tang K, Fang XL, Xu JX, Mao XY, Li M

SYSTEMATIC REVIEWS

- 1155** Quality-adjusted life years and surgical waiting list: Systematic review of the literature

de la Plaza Llamas R, Ortega Azor L, Hernández Yuste M, Gorini L, Latorre-Fragua RA, Díaz Candelas DA, Al Shwely Abduljabar F, Gemio del Rey IA

META-ANALYSIS

- 1165** Impact of different anastomosis methods on post-recurrence after intestinal resection for Crohn's disease: A meta-analysis

Wang ZZ, Zhao CH, Shen H, Dai GP

CASE REPORT

- 1176** Suspected coexistence of perianal necrotizing sweet syndrome in chronic myelomonocytic leukemia: A case report

Yu KQ, Li HX, Wu J

- 1184** Successful splenic artery embolization in a patient with Behçet's syndrome-associated splenic rupture: A case report

Zhu GZ, Ji DH

- 1189** Stercoral perforation of the cecum: A case report

Yu HC, Pu TW, Kang JC, Chen CY, Hu JM, Su RY

- 1195** Percutaneous transhepatic stenting for acute superior mesenteric vein stenosis after pancreaticoduodenectomy with portal vein reconstruction: A case report
Lin C, Wang ZY, Dong LB, Wang ZW, Li ZH, Wang WB
- 1203** Endoscopic treatment of bleeding gastric ulcer causing gastric wall necrosis: A case report
Li WF, Gao RY, Xu JW, Yu XQ
- 1208** Intermittent melena and refractory anemia due to jejunal cavernous lymphangioma: A case report
Liu KR, Zhang S, Chen WR, Huang YX, Li XG

LETTER TO THE EDITOR

- 1215** New frontiers in ectopic pancreatic tissue management
Covantsev S

ABOUT COVER

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WJGS mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal surgery and covering a wide range of topics including biliary tract surgical procedures, biliopancreatic diversion, colectomy, esophagectomy, esophagostomy, pancreas transplantation, and pancreatectomy, *etc.*

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Blastomas of the digestive system in adults: A review

Yu Liu, Tony El Jabbour, Jonathan Somma, Yukihiro Nakanishi, Saverio Ligato, Hwajeong Lee, Zhi-Yan Fu

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Abstract

Blastomas, characterized by a mixture of mesenchymal, epithelial, and undifferentiated blastematos components, are rare malignant neoplasms originating from precursor blast cells. This review focuses on digestive system blastomas in adult patients, including gastroblastoma, hepatoblastoma, and pancreatoblastoma. Gastroblastoma is a biphasic, epitheliomesenchymal tumor, with only sixteen cases reported to date. In addition to the characteristic histology, metastasis-associated lung adenocarcinoma transcript 1 - glioma-associated oncogene homolog 1 gene fusion is typical, although recently novel ewing sarcoma breakpoint region 1 - c-terminal binding protein 1 and patched 1 - glioma-associated oncogene homolog 2 fusions have been described. Hepatoblastoma is exceptionally rare in adults and can show a variety of histologic patterns which may cause diagnostic difficulty. Pancreatoblastoma, primarily a pediatric tumor, displays acinar differentiation and squamoid nests with other lines of differentiation also present, especially neuroendocrine. Diagnostic approaches for these blastomas include a combination of imaging modalities, histopathological examination, and molecular profiling. The treatment generally involves surgical resection, which may be supplemented by chemotherapy or radiotherapy in some cases. Prognoses vary with gastroblastoma generally showing favorable outcomes post-surgery whereas hepatoblastoma and pancreatoblastoma often have poorer outcomes, particularly in the setting of metastases. This review highlights the complexity of diagnosing and managing these rare adult blastomas as well as the need for ongoing research to better understand their pathogenesis and improve treatment strategies.

Key Words: Adult blastomas; Gastroblastoma; Hepatoblastoma; Pancreatoblastoma; Digestive system

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Core tip: Adult digestive system blastomas, including gastroblastoma, hepatoblastoma, and pancreatoblastoma, are rare neoplasms with less than a hundred cases reported for each type. They have nonspecific clinical presentations and imaging findings. Gastroblastoma diagnosis hinges on biphasic histology and the metastasis-associated lung adenocarcinoma transcript 1 - glioma-associated oncogene homolog 1 gene fusion. Hepatoblastoma recapitulates the different embryological stages of liver development and can be epithelial or mixed epitheliomesenchymal. Pancreatoblastoma demonstrates multidirectional differentiation and contains squamoid nests. Surgical resection is the primary treatment for these tumors with adjuvant chemotherapy or radiotherapy in some cases. Prognoses vary, with gastroblastoma typically having better post-surgical outcomes. In contrast, hepatoblastoma and pancreatoblastoma frequently recur and metastasize.

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INTRODUCTION

A blastoma is a malignant neoplasm consisting of a combination of mesenchymal, epithelial, and undifferentiated blastematos components. It originates from precursor cells called blasts. Blastomas arise at a variety of sites, and typical examples include medulloblastoma and neuroblastoma. However, the primary digestive system blastomas, hepatoblastoma, pancreatoblastoma, and gastroblastoma, are uncommon, and the literature on these tumors is limited, particularly for cases arising in adults. In fact, no comprehensive resource is presently available. Thus, we aim to present a thorough review of digestive system blastomas in adults which, among other things, will highlight up to date information regarding the complexity of diagnosis, molecular pathogenesis, and management.

Gastroblastoma is a rare tumor, first described by Miettinen *et al*[1] in 2009. It was added to the World Health Organization (WHO) Classification of Tumors of the Digestive System in 2019. Only sixteen cases have been reported to date, most occurring in young adults. However, six have been reported in patients over 30, and the oldest reported case was in a 74-year-old[2]. Gastroblastoma is an epitheliomesenchymal neoplasm primarily developing in the gastric body and antrum[3]. Diagnosis typically relies on the presence of the metastasis-associated lung adenocarcinoma transcript 1 - glioma-associated oncogene homolog 1 (*MALAT1-GLI1*) gene fusion and its biphasic (epitheliomesenchymal) histology[3]. However, recent discoveries, such as the ewing sarcoma breakpoint region 1 - c-terminal binding protein 1 (*EWSR1-CTBP1*) gene fusion in a patient with Wiskott-Aldrich syndrome[4] and the patched 1 - glioma-associated oncogene homolog 2 (*PTCH1-GLI2*) gene fusion[5,6], suggest more genetic diversity than was originally thought.

Hepatoblastoma accounts for 79% of all pediatric malignant liver tumors. Almost 90% of tumors appear before the age of 5, and only 3% occur in patients older than 15 years[7]. Adult hepatoblastoma was first reported by Marx[8] in 1904, and, to date, only about 75 cases of adult hepatoblastoma have been reported[9,10]. Compared to childhood hepatoblastoma, where the 5-year overall survival rates exceed 70%[11,12], adults have a high rate of mortality and poor prognosis, with a 1-year survival rate of 24%[13]. Frequently, patients present with an elevated serum alpha-fetoprotein (AFP) level, which can be used to monitor response to therapy[14]. Although the etiology and pathogenesis of hepatoblastoma are poorly understood, mutations in the β -catenin gene, which plays a critical role in the WNT signaling pathway, are commonly observed in both pediatric and adult cases[15]. Due to its rarity in adults, treatment is not as standardized as it is in children, but surgical management is the mainstay of therapy in both populations[12].

Pancreatoblastoma is a rare malignancy, accounting for less than 1% of all exocrine neoplasms of the pancreas[16]. It is characterized by a multilineage cellular proliferation predominantly showing acinar differentiation with distinctive squamoid nests often present. Additionally, neuroendocrine differentiation is common whereas ductal and mesenchymal components are less pronounced[17]. It is most prevalent in pediatric patients, comprising 25% of pancreatic neoplasms in children in the first decade of life[18]. In adults, however, pancreatoblastoma is uncommon, with an incidence rate of just 0.004 per 100000 individuals aged 19 and older, and less than 80 such cases have been reported in the literature to date[19-22]. The genetic landscape of pancreatoblastoma often involves somatic alterations, including the loss of chromosome 11p, which is also implicated in Beckwith-Wiedemann Syndrome, and mutations in the Wnt/ β -catenin signaling pathway[16,23,24]. Notably, the clinical course of pancreatoblastoma in adults is more aggressive than in children. Metastasis and/or invasion of adjacent structures contribute to 58% of adult pancreatoblastoma cases, leading to three-year survival rates of less than 40%. This sharply contrasts with the 94.4% 5-year overall survival observed in children[25-27].

CLINICAL MANIFESTATIONS

In most cases of gastroblastoma, adult patients present with non-specific symptoms and, in some, the diagnosis is incidental. Reported symptoms include fatigue, abdominal mass, abdominal and/or epigastric pain, and hematemesis [28]. Similarly, hepatoblastoma has non-specific initial clinical manifestations. Pain is the most common symptom including epigastric, abdominal, and low back pain. Fever, vomiting, nausea, anorexia/weight loss, and hepatomegaly/abdominal mass are also reported. Rarely described manifestations are gastrointestinal bleeding, dyspnea, and lower extremity edema [29]. Pancreatoblastoma is frequently asymptomatic early on; late manifestations include abdominal pain/mass, splenomegaly, obstructive jaundice, fever, diarrhea, melena, weight loss, and occult blood in urine [26].

LABORATORY/IMAGING FINDINGS

The imaging findings of blastomas are similar to those of more common tumors of the digestive system. Gastroblastomas appear heterogeneous on abdominal computed tomography (CT) [30], and magnetic resonance imaging (MRI) offers superior soft tissue contrast to clarify the tumor's extent and relationship to adjacent structures. Gastroendoscopy typically reveals an ulcerated, submucosal based mass [4,31]. Although not specific for gastroblastoma, serum markers like Carcinoembryonic Antigen and Carbohydrate Antigen 19-9 (CA19-9) can be elevated in some cases and can be helpful in monitoring for disease recurrence.

Hepatoblastoma may be detected as unifocal or multifocal lesions by imaging. On ultrasound, the tumor is reported as a hyperechoic and solid mass [32]. CT scans and MRIs provide superior delineation of tumor characteristics, extent, and vascular involvement. The use of contrast agents, particularly during the arterial phase, can highlight tumor vascularity. Serum AFP level is usually increased but nonspecific [10,33].

Pancreatoblastomas are single, large, well-delineated, circular or lobulated masses with scattered or aggregate calcifications visible on both CT and MRI. Heterogeneous character may reflect a cystic component of some tumors [34]. Contrast imaging shows enhancement in the arterial phase that can mimic a hypervascular neuroendocrine tumor [34-36]. Common bile duct involvement (*i.e.*, dilatation) is apparent in some pancreatic head tumors [34,35,37,38]. Serum AFP has been noted to be increased in 68% cases [18,39] and may be used to monitor the effectiveness of therapy [40]. In the case reported by Li *et al* [35], the patient showed elevated CA19-9 and Cancer Antigen 125 levels [35,38]. Rarely adrenocorticotrophic hormone can be secreted from the tumor [40-42].

CASE REPORTS

Table 1 summarizes adult gastroblastoma case reports from 2009 to present [43-48]. Patients were on average 37-years-old (range 19-74 years old) at the time of diagnosis. Surgical management was the primary treatment modality, and the gastric antrum was the most common tumor site. Molecular testing was not conducted in the majority of cases, but among those cases tested, all had the *MALAT1-GLI1* gene fusion except for one case with a *PTCH1-GLI2* gene fusion. Although reported follow-up times varied substantially, ranging from 3 months to 14 years, the clinical course was favorable in the majority of patients.

A total of 12 adult hepatoblastoma cases have been reported in the English literature from 2013 to 2023 (**Table 2**) [49-56]. The average age was 44 years old with a wide range from 22 to 84 years old, and tumors were more frequently right sided. Twelve cases demonstrated elevated serum AFP, and hepatitis B infection and liver cirrhosis were present in 40%. Metastasis at the time of disease presentation was infrequent. Histologically, 75% of cases exhibited mixed epithelial and mesenchymal patterns, and the remainder were purely epithelial. Surgical resection constituted the primary treatment modality, often followed by adjuvant chemotherapy. Follow-up periods were generally short. However, this may be due to the aggressive course of most patients; short term recurrence or metastasis and death were frequent outcomes.

A total of 47 adult pancreatoblastoma cases have been reported since 2018 (**Table 3**) [57-68]. The average age of affected individuals was 45 years old (range 19 to 75 years old). Half of the patients were diagnosed with metastasis at the time of initial diagnosis, typically to the liver. Tumors arose throughout the pancreas with no discernable pattern. Primary treatment modalities included surgical resection and chemotherapy. Follow-up ranged from several months to a few years, and, although many patients experienced disease recurrence or metastasis, there were several instances of better outcomes during the follow-up period.

HISTOPATHOLOGY

Histopathological assessment plays a pivotal role in the diagnosis of blastomas of the digestive system. Gastroblastomas arise within the gastric muscularis propria, and neither component of its biphasic histology displays much cytologic atypia (**Figure 1**). The epithelial component consists of cells with round uniform nuclei, slightly eosinophilic cytoplasm, and inconspicuous nucleoli. These cells are arranged in sheets, nests, cords, and tubules. Notably, the epithelial component in some cases forms gland- or rosette-like structures that may contain mucin or dense eosinophilic globules. In contrast, the mesenchymal component consists of homogeneous and slender spindle cells often embedded within a myxoid matrix [28,30]. Immunohistochemistry can be helpful in highlighting these components and confirming the

Table 1 Summary of reported cases of adult gastroblastoma

Ref.	Age/sex	Location	Molecular alteration (s)	Treatment	Follow-up	Recurrence or metastasis
Castri <i>et al</i> [43], 2019	74/M	Gastric antrum	<i>MALAT1::GLI1</i>	Partial gastrectomy	5 years	Recurrence after 5 years
Centonze <i>et al</i> [28], 2019	43/F	Gastric antrum	Not performed	Partial gastrectomy	100 months	No
Fernandes <i>et al</i> [44], 2014	19/F	Gastric antrum	Not performed	Partial distal gastrectomy	20 months	No
Graham <i>et al</i> [3], 2017	27/M	Stomach	<i>MALAT1::GLI1</i>	Partial gastrectomy	12 months	No
Graham <i>et al</i> [3], 2017	56/F	Stomach	<i>MALAT1::GLI1</i>	N/A	N/A	Metastasis to liver
McCammon <i>et al</i> [2], 2023	26/M	Gastric pylorus extending through the first and second portions of the duodenum	<i>MALAT1::GLI1</i>	Tumor resection from the mucosa of pylorus and duodenum	2 months	No
Miettinen <i>et al</i> [1], 2009	30/M	Gastric antrum	Not performed	Antrectomy, postoperative radiation	14 years	No
Miettinen <i>et al</i> [1], 2009	27/F	Gastric body	Not performed	Partial gastrectomy	5 years	No
Miettinen <i>et al</i> [1], 2009	19/M	Gastric body	Not performed	Subtotal gastrectomy	3.5 years	No
Pinto <i>et al</i> [31], 2019	53/F	Gastric antrum	Not performed	Partial gastrectomy	18 months	No
Poizat <i>et al</i> [45], 2012	22/F	Duodenum	Not performed	Partial resection of the distal duodenum	16 months	No
Toumi <i>et al</i> [46], 2017	29/F	Gastric body	Not performed	Partial gastrectomy + splenectomy	6 months	Local recurrence after 6 months
Wey <i>et al</i> [30], 2012	28/M	Distal stomach	<i>MALAT1::GLI1</i>	Preoperative chemotherapy + partial gastrectomy	3 months	Metastasis to lymph nodes, liver, pelvis; clinically stable at 3 months
Gong <i>et al</i> [47], 2023	19/M	Gastric antrum	No gene break rearrangement detected by FISH	Partial gastrectomy	19 months	No
Zhu <i>et al</i> [48], 2018	65/F	Gastric body	Not performed	Full-thickness resection of the gastric wall	4 years	No
Chen <i>et al</i> [5], 2022 and Liu <i>et al</i> [6], 2022	58/M	Gastric body	<i>PTCH1::GLI2</i>	Endoscopic submucosal dissection	1 year	No

F: Female; M: Male; N/A: Not available.

diagnosis. The epithelial component expresses various cytokeratins including AE1/AE3, Cytokeratin 7 (CK7), Cytokeratin 19 (CK19), CAM5.2, and epithelial membrane antigen (EMA). The spindle cells are negative for cytokeratin and express CD56 and CD10. Of diagnostic significance, gastroblastoma does not express CD117 antigen (KIT), Discovers on GIST-1 (DOG1), CD34, Smooth Muscle Actin (SMA), Desmin, synaptophysin, chromogranin, and S100, which separate it from other gastric neoplasms that may be considered in the histologic differential diagnosis[26,29]. Besides its biphasic differentiation, detection of *MALAT1-GLI1* gene fusion was traditionally regarded as confirmatory, although *EWSR1-CTBP1* (in a pediatric case[4]) and *PTCH1-GLI2* fusions have been described more recently[5,6].

The histology of hepatoblastoma may reflect any stage of hepatic development and, thus, can be quite varied. Some tumors are purely epithelial while others show mixed epithelial and mesenchymal differentiation. The epithelial elements can range in appearance from that of early immature embryonal hepatocytes to a well differentiated hepatocellular phenotype. When present, fetal-type cells are characterized by eosinophilic cytoplasm and distinct cell borders, often arranged in cords or nests reminiscent of, but disorganized as compared to normal liver architecture. In contrast, embryonal components appear more basophilic and densely packed, with a tendency to form pseudoacinar structures. Adding to the potential for diagnostic confusion, ductular (cholangioblastic) differentiation may also be found, and some cases show small cell undifferentiated (SCUD) histology. Mesenchymal components are also varied and can range from fibroblastic to heterologous elements such as bone or cartilage (Figure 2), and some tumors are divided into lobules by non-neoplastic fibrous bands[9,28,29,32,69,70]. There is no definitive immunomarker to distinguish hepatoblastoma from

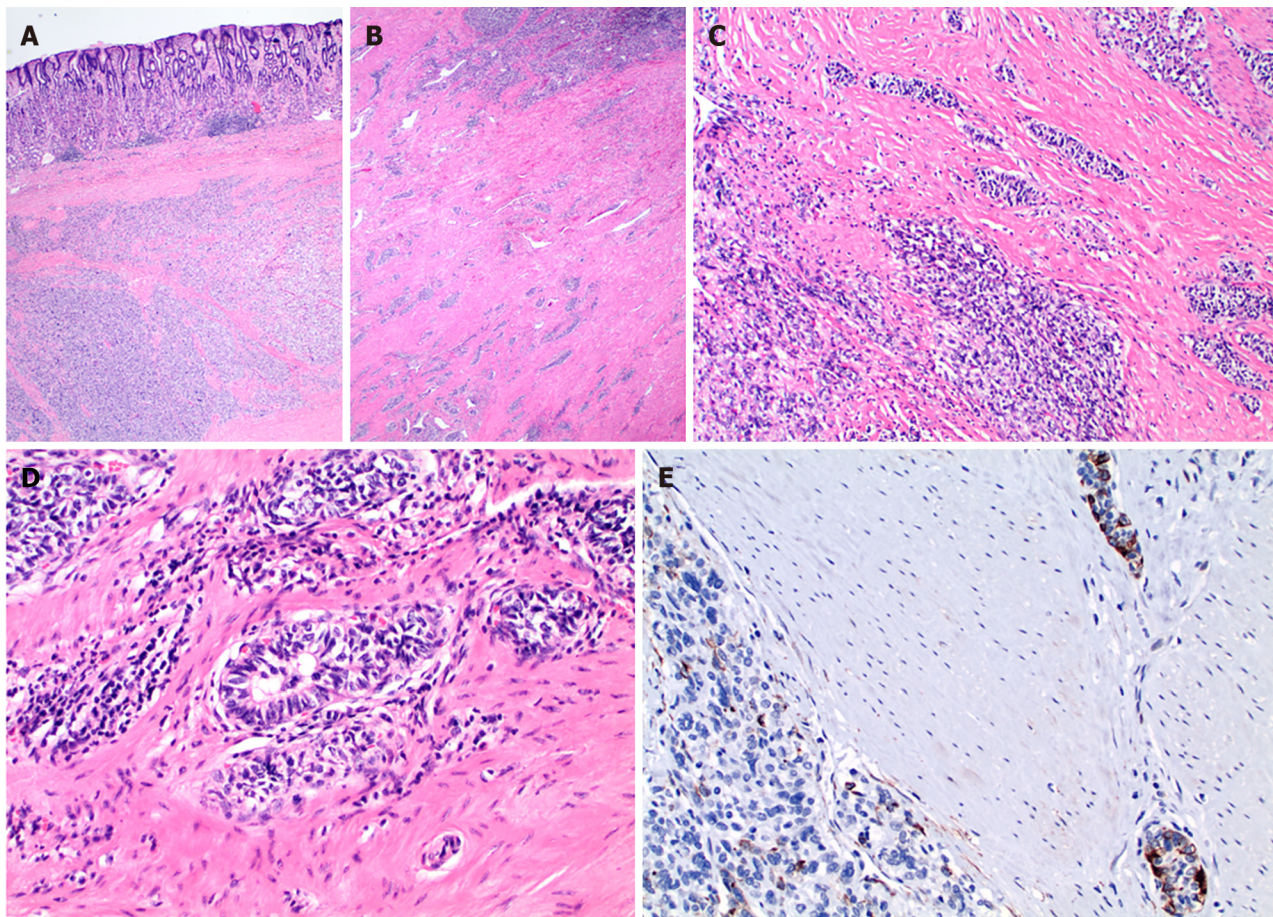


Figure 1 Gastroblastoma in a 19-year-old patient. A and B: The tumor involves the muscularis propria of the antrum (20 ×); C: The tumor shows a biphasic histology with spindle stromal component more prominent in left lower of the image (40 ×); D: The high-magnification image shows the epithelial cells with glandular formation (400 ×); E: Cytokeratin staining (AE1/3) labels the epithelial cells but not the mesenchymal component (200 ×).

hepatocellular carcinoma, although the latter is positive only for hepatocellular markers, usually occurs in a cirrhotic liver background, and will not contain immature or mesenchymal components. That said, immunohistochemical markers still play a role in the diagnostic and prognostic evaluation of hepatoblastoma[10,28,70,71] with at least some tumor cells, depending on their histologic appearance, expressing AFP, HepPar1, glypican 3, and/or β -catenin (nuclear and cytoplasmic). Pancytokeratins are variably positive in epithelial components, and CK7 and CK19 will highlight cholangio-blastic elements when present. Importantly, SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1 (SMARCB1/INI1) is expressed in almost all cases of hepatoblastoma, throughout its varied components. SMARCB1 negative tumors are rare, limited to a subset of those with SCUD histology, and have a poor prognosis.

Histology of adult pancreatoblastoma is characterized by a multilineage cellular proliferation predominantly showing acinar differentiation with distinctive squamoid nests always present. Additionally, neuroendocrine differentiation is common whereas ductal, mesenchymal, or more primitive components are less pronounced. Its acinar component can mimic acinar cell carcinoma as well as the related typical histologic differential diagnosis of pancreatic endocrine tumors and solid pseudopapillary neoplasms too. However, none of these display the prototypical squamoid nests of pancreatoblastoma[22]. While the neuroendocrine component of pancreatoblastoma may be detectable as increased serum levels of hormones, this is uncommon in the adult population[21]. Immunohistochemistry plays a critical role in diagnosing pancreatoblastoma. Acinar differentiation is highlighted with immunolabeling for trypsin, chymotrypsin, and B-cell Lymphoma/Leukemia 10. Neuroendocrine differentiation is evidenced by the expression of Synaptophysin, Chromogranin, and Insulinoma-Associated Protein 1, but should not be diffuse as in the case of pancreatic endocrine tumors. The squamoid component is positive for EMA and beta-catenin (nuclear staining) whereas the latter would be diffusely evident in a solid pseudopapillary neoplasm. Although these tumors may be histologically complex, the synchronous presence of acinar differentiation with immunochemical confirmation plus squamoid nests typically allows for straightforward diagnosis in well sampled tumors[22] (Figure 3).

MOLECULAR PATHOLOGY

A molecular hallmark of adult gastroblastoma is the *MALAT1-GLI1* fusion, which is considered essential for diagnosis

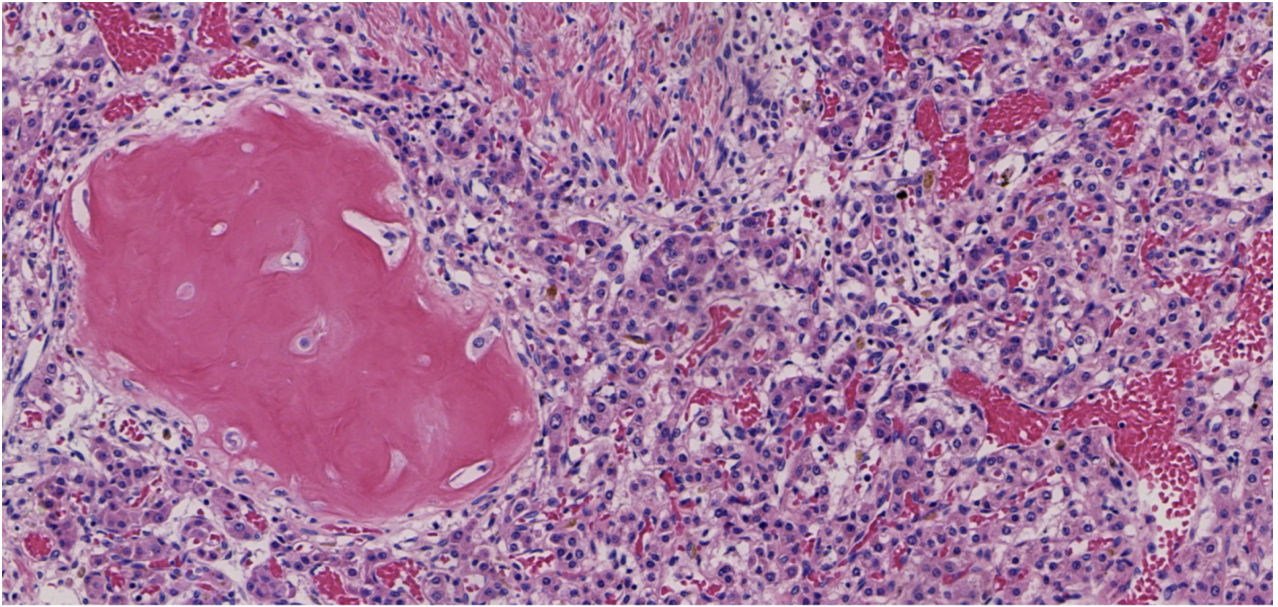


Figure 2 Mixed epithelial mesenchymal hepatoblastoma in an adult patient, showing a heterogeneous mix of epithelial and mesenchymal components. Well differentiated fetal-type epithelial component is characterized by their eosinophilic cytoplasm and cords or nests-like growth reminiscent of normal liver architecture. The mesenchymal part shows heterologous osteoid elements (100 ×).

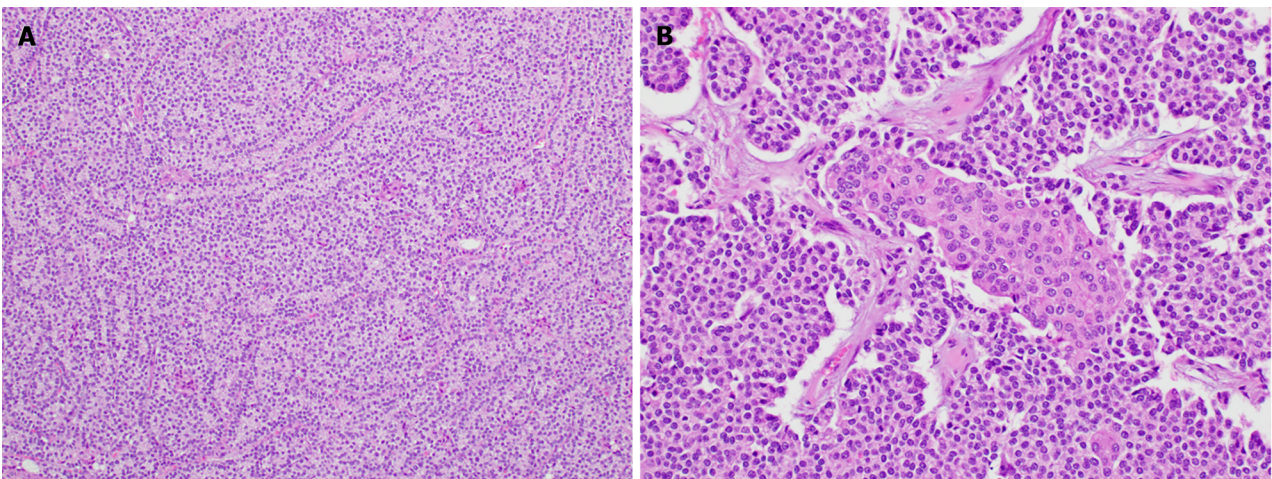


Figure 3 Pancreatoblastoma in the pancreatic head of a 42-year-old male patient. A: The tumor is composed of acinar and ribbonlike morphology composed of relatively monotonous cells with basophilic nuclei, mimicking a pancreatic endocrine tumor (100 ×); B: In a few foci, squamoid nests, consisting of circumscribed whorled nests of polygonal cells with abundant eosinophilic cytoplasm and a squamous appearance, are present (200 ×).

according to the 2019 WHO classification of digestive system tumors[3]. However, recent literature calls this into question. A pediatric patient with Wiskott-Aldrich syndrome, reported by Koo *et al*[4] in 2021, presented with a gastric submucosal tumor. Despite showing typical histological and immunohistochemical features of gastroblastoma, molecular analysis revealed an *EWSR1-CTBP1* fusion gene. Chen *et al*[5] recently identified a *PTCH1::GLI2* gene fusion in another adult patient with otherwise prototypical gastroblastoma[5,6]. Both cases showed no evidence of the *MALAT1-GLI1* fusion. These genes, *PTCH1* and *GLI2*, are integral to the Hedgehog (Hh) signaling pathway, which plays a vital role in embryonic development[5,6]. These reports suggest a broader spectrum of genetic aberrations in gastroblastoma than was previously thought.

Genomic sequencing studies have established that mutations in the Wnt- β -catenin signaling pathway are prevalent in hepatoblastoma, with alterations in the Catenin Beta 1 (*CTNNB1*) gene detected in about 90% of cases[15,72]. These mutations are central to disease pathogenesis and are often accompanied by changes in other Wnt signaling genes. Additionally, a subpopulation of high-risk hepatoblastomas exhibits alterations in the Nuclear Factor, Erythroid 2 Like 2 (*NFE2L2*) gene, indicating oxidative stress as a contributing factor to cellular transformation and disease progression. The Yap signaling pathway collaborates with β -catenin in tumor development. Nevertheless, the activation mechanism of Yap in hepatoblastoma cases is still unclear, necessitating further studies[72]. Such molecular profiling highlights the complex genetic landscape of hepatoblastoma, may impact patient management presently, and potentially has implications for

Table 2 Summary of reported cases of adult hepatoblastoma from recent 10 years (2013-2023)

Ref.	Age/sex	Location	Hepatitis B	Liver cirrhosis	AFP	Metastasis at diagnosis	Histology	Treatment	Follow-up	Recurrence or metastasis
Pagarigan <i>et al</i> [49], 2023	49/F	Right hepatic lobe	HBsAg (+); anti-HBc (+)	Yes	> 50000 ng/mL	No	Mixed	Surgical resection + postoperative chemotherapy	4 months	Recurrence
Ihssan <i>et al</i> [10], 2022	26/F	Right Hepatic lobe	No	No	2275 ng/mL	No	Epithelial (the mixed fetal and embryonic pattern)	Surgical resection	N/A	N/A
Ihssan <i>et al</i> [10], 2022	50/M	Entire liver	No	No	6386 ng/mL	No	Mixed	N/A	N/A	N/A
Park <i>et al</i> [50], 2015	36/F	Right hepatic lobe	HBsAg (+); anti-HBc (+)	Yes	676.5 ng/mL	No	Mixed	Surgical resection + postoperative chemotherapy	5 months	Intraperitoneal metastasis, died
Caso-Maestro <i>et al</i> [51], 2013	27/M	Right hepatic lobe	HBsAg +, HBcAb +, HBeAb +	No	1166000 ng/mL		Mixed	Surgical resection	27 months	Left adrenal recurrence followed by total adrenalectomy; alive
Al-Jiffry <i>et al</i> [33], 2013	22/M	Left hepatic lobe	No	No	Normal	Diaphragm, pericardial, and IVC infiltration	Mixed	Surgical resection	16 d	Died
Cienfuegos <i>et al</i> [52], 2013	37/F	Segment 5 and 6 of the liver	HBsAg +, HBcAb +, HBeAb +	Yes	1556.3 ng/mL	No	Mixed	Surgical resection	10 months	Recurrence and died
Zhang <i>et al</i> [53], 2013	32/F	Left hepatic lobe	No	No	Normal	No	Epithelial, neuroendocrine differentiation	N/A	N/A	N/A
Park <i>et al</i> [50], 2015	36/F	Right hepatic lobe	HBsAg +, HBcAb +, HBeAb +		676.5 ng/mL	No	Mixed	Surgical resection + postoperative chemotherapy	12 months	Left subphrenic area metastasis; died
Celotti <i>et al</i> [54], 2016	68/M	Left hepatic lobe	No	No	1231 ng/mL	Pericardial metastasis	Mixed	Left lobectomy +; diaphragm resection + extended pericardiectomy	21 months	No recurrence
Urdiain <i>et al</i> [55], 2019	65/M	Right hepatic lobe	No	No	N/A	No	Epithelial	Surgical resection	10 months	Recurrence, died
Dave <i>et al</i> [56], 2019	84/M	Left hepatic lobe	N/A	N/A	708 IU/mL	Metastatic to left lower bronchus, left descending pulmonary artery and left descending pulmonary vein	Mixed	N/A	N/A	N/A

AFP: Alpha-fetoprotein; F: Female; M: Male; HBsAg: Hepatitis B surface Antigen; HBcAb: Hepatitis B core antibody; HBeAb: Hepatitis B e-antibody; N/A: Not available; IVC: Inferior vena cava.

targeted therapy in the future.

Adult pancreatoblastomas exhibit loss of heterozygosity on chromosome 11p in 86% of cases and alterations in the APC/ β -catenin signaling pathway in 67% of cases, including biallelic inactivation of *APC* and activating *CTNNB1* mutations[23]. Interestingly, there is an overlap here with the molecular pathology of hepatoblastoma. Most recently, studies have identified alterations in the Fibroblast Growth Factor Receptor (FGFR) signaling pathway, including *FGFR1* mutations and *FGFR2* rearrangements, in pancreatoblastomas[64]. Additionally, high-level amplification of Myeloid Cell Leukemia Sequence 1 (*MCL1*) has been identified in a small percentage of pancreatoblastoma patients. The patients with *MCL1*-amplified pancreatoblastoma could potentially benefit from targeted *MCL1* inhibition[73].

Table 3 Summary of reported cases of adult pancreatoblastoma from recent 5 years (2018-2023)

Ref.	Age/sex	Location	Metastasis before treatment	Treatment	Follow-up (months/years)	Recurrence/metastasis	Outcome
Rojas <i>et al</i> [22], 2023	45/F	Pancreatic tail	No	Pancreatectomy and splenectomy; Chemotherapy; stem cell transplant	3 months	Liver metastasis	N/A
Machado <i>et al</i> [57], 2023	3 patients (2F, 1M); avg age: 51	Tail and body of pancreas	Liver and lung metastasis	Surgical resection	6 years 2 months	Regional or distant metastasis	2 died; 1 alive after 6 years 2 months following surgery
Hussain and Farrukh [58], 2023	75/M	Pancreatic head	Liver metastasis	Chemotherapy; stent insertion	5 months	No	Stable
Wu <i>et al</i> [34], 2022	7 patients (2M, 5F); avg age: 56.71	Pancreatic head (<i>n</i> = 3), tail (<i>n</i> = 2), gastric antrum (<i>n</i> = 1), neck (<i>n</i> = 1)	Liver (<i>n</i> = 2), Lymph node (<i>n</i> = 2), kidney adrenal (<i>n</i> = 1)	N/A	Not reported in 3 cases, 24, 26, 4, 4 months in others	N/A	4 patients died during follow-up
Suemitsu <i>et al</i> [59], 2021	74/M	Tail of pancreas	No	Open distal pancreatectomy and splenectomy	36 months	No	Recurrence-free
Li <i>et al</i> [35], 2021	60/F	Tail of the pancreas	Right liver metastasis	Resection and chemotherapy	16 months	N/A	Death
Morales <i>et al</i> [20], 2021	76/M	Pancreatic head	Lymphovascular and perineural invasion	Chemotherapy	32 months	No	Stable
Raoul <i>et al</i> [60], 2021	33/F	Pancreas	Invading gastric wall	Pancreatectomy, Chemotherapy	14 months	Liver metastasis	Stable
Raoul <i>et al</i> [60], 2021	33/F	Pancreatic tail	Liver metastasis	Chemotherapy	20 months	No	Stable
Elghawry <i>et al</i> [61], 2021	23/F	Pancreatic tail	Liver metastasis	Chemotherapy; autologous hematopoietic cell transplant	57 months	N/A	Stable
Zhang <i>et al</i> [36], 2020	7 patients (7M); Avg age: 44.71	Pancreatic head (<i>n</i> = 3), neck (<i>n</i> = 1), body (<i>n</i> = 1), tail (<i>n</i> = 2)	Only 1 patient liver metastasis	Surgical resection	1.5 months, 6 months, 8 months, 8.5 months, 10 months, 2 years, 4 years	3 patients developing liver metastasis	Alive = 2, lost to follow-up = 5
Snyder <i>et al</i> [62], 2020	28/F	N/A	Liver metastasis	Chemotherapy; left suboccipital craniotomy	More than 51 months	Brain metastasis	Alive
Morrissey <i>et al</i> [63], 2020	69/M	Pancreatic head	No	Adjuvant chemotherapy; Surgical resection	10 weeks	No	Alive (tumor-free)
Berger <i>et al</i> [64], 2020	32/F	Pancreatic head	Liver metastasis	Pancreaticoduodenectomy and Lymphonodectomy; Right hemihepatectomy for liver metastasis; Chemotherapy	14 months	Lung metastasis	Died
Berger <i>et al</i> [64], 2020	19/M	Pancreas	No	Chemotherapy, pylorus-preserving pancreaticoduodenectomy; autologous stem cell transplantation	24 months	Liver and abdominal lymph node metastasis	Died
Berger <i>et al</i> [64], 2020	30/M	Pancreatic head	No	Complete pancreatectomy; adjuvant chemotherapy; Immunotherapy	17 months	Liver metastasis	Died
Berger <i>et al</i> [64], 2020	20/F	Pancreatic tail	Diffuse liver metastasis	Chemotherapy	14 months	N/A	Died

Liu <i>et al</i> [65], 2020	49/M	Pancreatic tail	Liver metastasis	Complete resection of the primary and metastatic lesions.	2 years	N/A	Stable
Yin <i>et al</i> [66], 2019	27/F	Pancreatic head	No	Pancreatoduodenectomy	1 year and 10 months	Liver metastasis	Alive
Reid <i>et al</i> [67], 2019	11 adults (6M, 5F); median age: 45	Pancreatic head (<i>n</i> = 7), tail (<i>n</i> = 4)	3 patients, location N/A	Not mentioned in detail; suggestive of surgical resection	Average 39.8 months	4 cases developing metastasis	Alive = 6, died = 5
Chen <i>et al</i> [19], 2018	26/M	Head of pancreas	Liver metastasis	TACE	4 years	No	Died
Yamaguchi <i>et al</i> [24], 2018	37/F	Pancreas head	No	Pancreaticoduodenectomy and chemotherapy	13 months	Liver metastasis	Died
Nunes <i>et al</i> [68], 2018	31/M	Pancreatic tail	Liver metastasis	Hemodialysis	3 months	N/A	Died

TACE: Transcatheter hepatic arterial chemoembolization; N/A: Not available; M: Male; F: Female.

TREATMENT AND PROGNOSIS

Surgical resection is the primary treatment approach in all blastomas of the digestive system with chemotherapy or radiotherapy considered for some patients. Generally, post-surgical outcomes are favorable in adult gastroblastoma patients. However, in some cases, local recurrence, metastasis, and death have been reported[30,43]. The case report by Liu *et al*[6] demonstrating successful treatment with endoscopic submucosal dissection offers an insight into less invasive treatment for localized disease[6].

Outcomes are markedly different in adult hepatoblastoma. For unresectable tumors, the one-year survival rate is 0% whereas it is 41% for resectable tumors[69]. Prognosis is dependent on various factors including patient age, extent of resection, and stage of disease. Outcomes are much better in patients who had complete surgical resection before the age of 45 years compared to those who were treated after that[69]. Adjunctive chemotherapy including vincristine, 5-fluorouracil, and cisplatin have improved the 5-year survival rate[69].

Adult pancreatoblastoma, even with aggressive therapy, has poor outcomes and its optimal treatment strategy is not known. While controversial, adjuvant chemotherapy, including 5-fluorouracil/doxorubicin/mitoycin and dorubicin/carboplatin, and radiotherapy may be used as palliative treatment in advanced disease[41]. The average survival in adults is only 15-18 months[37,41]. Nearly half of patients have either local invasion and/or metastasis at diagnosis[41]. The most common site for metastasis is the liver, followed by regional lymph nodes and lung[41]. BRAF and MEK inhibitors such as Dabrafenib and Trametinib showed transient response at advanced stage, given the novel IQ Motif and Sec7 Domain 1 - Rapidly Accelerated Fibrosarcoma 1 (*IQSEC1-RAF1*) fusion in pancreatoblastoma[74].

COMPARISON OF DIGESTIVE SYSTEM BLASTOMA IN PEDIATRIC AND ADULT POPULATIONS

To date, only 16 cases of gastroblastoma in adults have been reported. Acknowledging the limited number of cases available for comparison, pediatric patients tend to present with more pronounced clinical symptoms, such as intermittent blood in stools and significant abdominal pain[75-77]. Moreover, a distinctive demographic difference is apparent, with all reported pediatric cases occurring in males[4,75-77], as opposed to adult gastroblastoma, which affects both males and females. The remaining disease features are consistent between the two populations, and, regardless of age, patients generally show a favorable prognosis following surgical resection.

Hepatoblastoma exhibits distinct characteristics in adults. Pediatric patients typically show symptoms like abdominal swelling and pain, whereas adult symptoms are subtler[69]. Notably, about 40% of adult cases from 2013 to 2023 have underlying liver conditions like viral hepatitis or cirrhosis (Table 2), unlike the pediatric cases, which generally occur in patients without pre-existing liver disease. Histologically, adult cases also often show a more aggressive, undifferentiated histology whereas pediatric hepatoblastoma tends to show more typical epithelial and mesenchymal components including heterologous elements that indicate a favorable prognosis[69,78,79]. In adult hepatoblastoma, the presence of embryonal or undifferentiated cells often indicates a poorer prognosis[69]. Most significantly, adults are more prone to recurrence or metastasis than children despite similar treatment approaches.

Pancreatoblastoma certainly shows significant differences between adults and children. Because only 17% of pediatric cases demonstrate extrapancreatic disease at the time of diagnosis[80], presenting symptoms, like abdominal pain, palpable abdominal masses, jaundice, and vomiting, are all attributable to local tumor effect. In contrast, adults have a poorer prognosis and often present with symptoms and signs related to the more aggressive disease course, which includes frequent invasion of adjacent organs and structures as well as frequent metastases. Histology is similar in the age groups, but adult pancreatoblastomas typically contain less stroma[81]. Surgical resection is the primary treatment for both groups, often supplemented with chemotherapy and radiation therapy. However, adults generally have a poorer

prognosis, frequently due to the invasion of adjacent organs or metastasis at the time of diagnosis.

CONCLUSION

In this review, we focus on adult digestive system blastomas, covering aspects like histopathology, molecular pathology, and treatment outcomes, along with comparisons between pediatric and adult cases. Gastroblastoma is characterized by biphasic morphology and distinctive genetic features, notably the *MALAT1-GLI1* fusion. Hepatoblastoma shows diverse morphology and commonly exhibits mutations in the Wnt- β -catenin signaling pathway. Pancreatoblastoma is marked by acinar differentiation and squamoid nests, sharing molecular pathology similarities with hepatoblastoma. Treatment mainly involves surgery, possibly with adjunct chemotherapy or radiotherapy. This review underscores the importance of ongoing research for a deeper understanding and improved management of these rare blastomas.

FOOTNOTES

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