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Blastomas of the digestive system in adults: A review

Review of adult GI blastomas

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Abstract

A blastoma is a malignant neoplasm consisting of a combination of mesenchymal, epithelial, and undifferentiated blastematous 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* in 2009[1]. 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 in 1904 [8], 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 100,000 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 (BWS), 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 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 (CEA) and 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. Heterogenous 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*, the patient showed elevated Carbohydrate Antigen 19-9 (CA19-9) and Cancer Antigen 125 (CA-125) levels [35, 38]. Rarely adrenocorticotropic hormone (ACTH) can be secreted from the tumor [40-42].

CASE REPORTS

Table 1 summarizes adult gastroblastoma case reports from 2009 to present. 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.

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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). 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). 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 matrixv[28, 30]. Immunochemistry can be helpful in highlighting these components and confirming the 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), Discovered 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 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 alpha-fetoprotein (AFP), HepPar1, glypican 3, and/or β-catenin (nuclear and cytoplasmic). Pancytokeratins are variably positive in epithelial components, and CK7 and CK19 will highlight cholangioblastic 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 (BCL10). Neuroendocrine differentiation is evidenced by the expression of Synaptophysin, Chromogranin, and Insulinoma-Associated Protein 1 (INSM1), 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].

MOLECULAR PATHOLOGY

A molecular hallmark of adult gastroblastoma is the *MALAT1-GLI1* fusion, which is considered essential for diagnosis 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 and no evidence of the *MALAT1-GLI1* fusion. Chen *et al* 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 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].

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* demonstrating successful treatment with endoscopic submucosal dissection (ESD) 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 pancreatobastoma, even with aggressive therapy, has poor outcomes and its optimal treatment strategy is not known. While controversial, adjuvant chemotherapy, including 5-flurororacil/doxorubicin/mitoycin and dororubicin/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.

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 (*MALAT1-GLI1*) 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.

INTRODUCTION

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The imaging findings of blastomas are similar to those of more common tumors of the digestive system. Gastroblastomas appear heterogeneous on abdominal 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 (CEA) and 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. Heterogenous 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*, the patient showed elevated Carbohydrate Antigen 19-9 (CA19-9) and Cancer Antigen 125 (CA-125) levels [35, 38]. Rarely adrenocorticotropic hormone (ACTH) can be secreted from the tumor [40-42].

CASE REPORTS

Table 1 summarizes adult gastroblastoma case reports from 2009 to present. 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.

Table 1 Summary of Reported Cases of Adult Gastroblastoma

First author and year	**Age/Sex**	**Location**	**Molecular alteration(s)**	**Treatment**	**Follow-up**	**Recurrence or Metastasis**
Castri 2019 [43]	74 M	Gastric antrum	*MALAT1::GLI1*	Partial gastrectomy	5 years	Yes, recurrence at 5 years
Centonze 2019 [28]	43 F	Gastric antrum	Not performed			

Partial gastrectomy

100 months

No

Fernandes 2014

[44]

19 F

Gastric antrum

Not performed

Partial distal gastrectomy

20 months

No

Graham 2017

[3]

27 M

Stomach

MALAT1::GLI1

Partial gastrectomy

12 months

No

Graham 2017

[3]

56 F

Stomach

MALAT1::GLI1

N/A

N/A

Metastasis to liver

McCammon

2023[2]

26 M

Gastric pylorus and the first and second portions of the duodenum.

MALAT1::GLI1

Tumor resection from the mucosa of pylorus and duodenum

2 months

No

Miettinen 2009

[1]

30 M

Gastric antrum

Not performed

Antrectomy, postoperative radiation

14 years

No

Miettinen 2009

[1]

27 F

Gastric body

Not performed

Partial gastrectomy

5 years

No

Miettinen 2009

[1]

19 M

Gastric body

Not performed

Subtotal gastrectomy

3.5 years

No

Pinto 2019

[31]

53 F

Gastric antrum

Not performed

Partial gastrectomy

18 months

No

Poizat 2012

[45]

22 F

Duodenum

Not performed

Partial resection of the distal duodenum

16 months

No

Toumi 2017

[46]

29 F

Gastric body

Not performed

Partial gastrectomy+splenectomy

6 months

Local recurrence after 6 months

Wey 2012

[30]

28 M

Distal stomach

*MALAT1::GLI1**

Preoperative chemotherapy+partial gastrectomy

3 months

Metastasis to lymph nodes, liver, pelvis; clinically stable at 3 months

Gong 2023

[47]

19 M

Gastric antrum

No gene break rearrangement detected by FISH

partial gastrectomy

19 months

No

Zhu 2018

[48]

65 F

Gastric body

Not performed

Full-thickness resection of the gastric wall

4 years

No

Chen 2022[5, 6]

58 M

Gastric body

PTCH1::GLI2

Endoscopic submucosal dissection

1 year

No

A total of 12 adult hepatoblastoma cases have been reported in the English literature from 2013 to 2023 (Table 2). 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.

Table 2 Summary of Reported Cases of Adult Hepatoblastoma from Recent 10 years (2013-2023)

First author and year

Age/Sex

Location

Hepatitis B

Liver cirrhosis

AFP

Metastasis at diagnosis

Histology

Treatment

Follow-up

Recurrence or Metastasis

Pagarigan

2023

[49]

49 F

Right hepatic lobe

HBsAg (+); anti-HBc (+)

Yes

>50,000 ng/mL

No

Mixed

Surgical resection+ postoperative chemotherapy

4 months

Recurrence

Ihssan2022

[10]

26 F

Right Hepatic lobe

No

No

2275 ng/mL

No

Epithelial (the mixed fetal and embryonic pattern)

Surgical resection

N/A

N/A

Ihssan2022

[10]

50 M

Entire liver

No

No

6386 ng/mL

No

Mixed

N/A

N/A

N/A

Park

2015

[50]

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 2013

[51]

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 2013

[33]

22 M

Right hepatic lobe

No

No

Normal

Diaphragm and pericardial infiltration; IVC infiltration

Mixed

Surgical resection

16 days

Died

Cienfuegos 2013

[52]

37 F

Segment 5 and 6 of the liver

HBsAg +, HBcAb +, HBeAb +

Yes

1556.3ng/mL

No

Mixed

Surgical resection

10 months

Recurrence and died

Zhang 2013

[53]

32 F

Left hepatic lobe

No

No

Normal

No

Epithelial, neuroendocrine differentiation

N/A

N/A

N/A

Park

2014

[50]

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

Celotti2016

[54]

68 M

Left hepatic lobe

No

No

1231 ng/mL

Pericardial metastasis

Mixed

Left lobectomy + diaphragm resection +extended pericardiectomy

21 months

No recurrence

Urdiain 2016

[55]

65 M

Right hepatic lobe

No

No

N/A

No

Epithelial

Surgical resection

10 months

Recurrence , died

Dave 2019

[56]

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

A total of 47 adult pancreatoblastoma cases have been reported since 2018 (Table 3). 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.

Table 3 Summary of Reported Cases of Adult Pancreatoblastoma from Recent 5 years (2018-2023)

First author and year

Age/Sex

Location

Metastasis before treatment

Treatment

Follow-up (months/years)

Recurrence/ metastasis

Outcome

Rojas 2023 [22]

45 F

Pancreatic tail

No

Pancreatectomy and splenectomy; Chemotherapy;

stem cell transplant

3 months

Liver metastasis

N/A

Machado 2023 [57]

3 patients ;2 female,1 male; 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 2023 [58]

75 M

Pancreatic head

Liver metastasis

Chemotherapy; stent insertion

5 months

No

Stable

Wu 2022 [34]

7 patients; 2 males, 5 females; Avg age: 56.71

Pancreatic head (*n* = 3), tail (*n* = 2), gastric antrum (*n* = 1), neck (*n* = 1)

Liver (*n* = 2), Lymph node (*n* = 2), kidney adrenal (*n* = 1)

N/A

Not reported in 3 cases, 24, 26, 4, 4 months in others

N/A

4 patients died during follow-up

Suemitsu 2021 [59]

74 M

Tail of pancreas

No

Open distal pancreatectomy and splenectomy.

36 months

No

Recurrence-free

Li 2021 [35]

60 F

Tail of the pancreas

Right liver metastasis

Resection and chemotherapy

16 months

N/A

Death

Molrales 2021[20]

76 M

Pancreatic head

Lymphovascular and perineural invasion

Chemotherapy

32 months

No

Stable

Roul 2021 [60]

33 F

Pancreas

Invading gastric wall

Pancreatectomy, Chemotherapy

14 months

Liver metastasis

Stable

Roul 2021 [60]

33 F

Pancreatic tail

Liver metastasis

Chemotherapy

20 months

No

Stable

Elghawy 2021 [61]

23 F

Pancreatic tail

Liver metastasis

Chemotherapy; autologous hematopoietic cell transplant

57 months

N/A

Stable

Zhang 2020 [36]

7 patients; all were males; Avg age: 44.71

3 in pancreatic head; 1 in neck; 1 in body; 2 in tail

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 2020 [62]

28 F

-

Liver metastasis

Chemotherapy; left suboccipital craniotomy

More than 51 months

Brain metastasis

Alive

Morrissey 2020 [63]

69 M

Pancreatic head

No

Adjuvant chemotherapy; Surgical resection

10 wk

No

Alive (tumor-free)

Berger 2020 [64]

32 F

Pancreatic head

Liver metastasis

Pancreaticoduodenectomy and Lymphonodectomy; Right hemihepatectomy for liver metastasis; Chemotherapy

14 months

Lung metastasis

Died

Berger 2020 [64]

19 M

Pancreas

No

Chemotherapy, pylorus-preserving pancreaticoduodenectomy; autologous stem cell transplantation

24 months

Liver and abdominal lymph node

metastasis

Died

Berger 2020 [64]

30 M

Pancreatic head

No

Complete pancreatectomy; Adjuvant chemotherapy: Immunotherapy

17 months

Liver metastasis

Died

Berger 2020 [64]

20 F

Pancreatic tail

Diffuse liver metastasis

Chemotherapy

14 months

N/A

Died

Liu 2020 [65]

49 M

Pancreatic tail

Liver metastasis

Complete resection of the primary and metastatic lesions.

2 years

N/A

Stable

Yin 2019 [66]

27 F

Pancreatic head

No

Pancreatoduodenectomy

1 year and 10 months

Liver metastasis

Alive

Reid 2019 [67]

11 adults; 6 (M), 5 (F); median age, 45 years

Pancreatic head (*n* = 7), tail (*n* = 4)

3 patients

Not mentioned in detail; suggestive of surgical resection

Average 39.8 months

4 cases developing metastasis

Alive=6, Died=5

Chen 2018 [19]

26 M

Head of pancreas

Liver metastasis

Transcatheter hepatic arterial chemoembolization (TACE)

4 years

No

Died

Yamaguchi 2018 [24]

37 F

Pancreas head

No

Pancreaticoduodenectomy and chemotherapy

13 months

Liver metastasis

Died

Nunes 2018 [68]

31 M

Pancreatic tail

Yes

Hemodialysis

3 months

N/A

Died

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 matrixv[28, 30]. Immunochemistry can be helpful in highlighting these components and confirming the 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), Discovered 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].

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

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 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 alpha-fetoprotein (AFP), HepPar1, glypican 3, and/or β-catenin (nuclear and cytoplasmic). Pancytokeratins are variably positive in epithelial components, and CK7 and CK19 will highlight cholangioblastic 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.

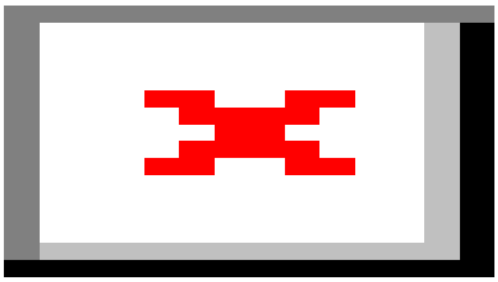

Figure 2 Mixed epithelial mesenchymal hepatoblastoma in an adult patient, showing a heterogeneous mix of epithelial and mesenchymal components. Well differentiated fetal-type epithelial component is characterized by their eosinophilic cytoplasm and cords or nests-like growth reminiscent of normal liver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

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 (BCL10). Neuroendocrine differentiation is evidenced by the expression of Synaptophysin, Chromogranin, and

Insulinoma-Associated Protein 1 (INSM1), 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 Pancreatoblastoma in the pancreatic head of a 42-year-old male patient. 3A: The tumor is composed of acinar and ribbonlike morphology composed of relatively monotonous cells with basophilic nuclei, mimicking a pancreatic endocrine tumor (100X); 3B: In a few foci, squamoid nests, consisting of circumscribed whorled nests of polygonal cells with abundant eosinophilic cytoplasm and a squamous appearance, are present (200x).

MOLECULAR PATHOLOGY

A molecular hallmark of adult gastroblastoma is the *MALAT1-GLI1* fusion, which is considered essential for diagnosis 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 and no evidence of the *MALAT1-GLI1* fusion. Chen *et al* 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 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].

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* demonstrating successful treatment with endoscopic submucosal dissection (ESD) 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 pancreatobastoma, even with aggressive therapy, has poor outcomes and its optimal treatment strategy is not known. While controversial, adjuvant chemotherapy, including 5-flurororacil/doxorubicin/mitoycin and dororubicin/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.

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