Pediatric Gastrointestinal Stromal Tumors and Neuroendocrine Tumors

Advances in Surgical Management

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KEYWORDS

• NET • Neuroendocrine tumors • GIST • Gastrointestinal stromal tumors • Pediatric oncology • Pediatric surgery

KEY POINTS

- Gastrointestinal stromal tumors (GIST) and neuroendocrine tumors (NET) in adult and pediatric populations differ immensely.
- Despite these established differences, the extreme rarity of GIST and NET in the pediatric population has resulted in the lack of consensus management guidelines, making optimal surgical approaches unclear.
- Surgery is adopted as the mainstay treatment for both pediatric GIST and NET with optimal approaches depending on tumor site.
- Pediatric GIST involves chronic management of disease burden to preserve quality of life as disease progression is often indolent with low mortality rates.
- Pediatric NET requires multi-disciplinary management with extensive long term follow-up and frequent screening.

INTRODUCTION

Gastrointestinal stromal tumors (GIST) and neuroendocrine tumors (NET) are extremely rare within the pediatric population. Although it is possible for GIST and

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NET to occur simultaneously, this is exceedingly rare with only one published case in the literature.[1] Accordingly, these malignancies usually occur in isolation. Comprehensive management principles to guide surgical approaches in adult literature are extensive. However, these are still lacking for pediatric patients. As such, this review individually highlights the unique differences between adult and pediatric subtypes in GIST and NET, which sheds light on the pressing need for standardized management principles specific to these young patients. At the same time, we offer insights into surgical approaches that may be adopted when encountering pediatric patients with these uncommon malignancies.

GASTROINTESTINAL STROMAL TUMORS IN CHILDREN

GIST are neoplasms of mesenchymal origin that are believed to arise from interstitial cells of Cajal or their precursors.[2] In the current literature, three subtypes exist: (1) adult GIST; (2) pediatric or wild-type GIST (P/WT-GIST); and (3) most recently described, young adult GIST.[3] Unlike their counterparts, P/WT-GIST are distinct in almost all facets, expressing differences in clinical behavior, molecular profile, prognosis, and therapeutic sensitivities.[4–7] Despite this, current management approach is adapted from adult guidelines because of the lack of principles specific to P/WT-GIST.[8–10] This is partly explained by the extreme rarity of P/WT-GIST, which is approximated by Surveillance, Epidemiology, and End Results and other reports to be 0.02 to 0.11 cases per million annually.[11,12] Because the exact incidence is unknown, this poses an extreme challenge for consolidation and preparation of a centralized management strategy. Consequently, because of the lack of understanding and universal guidelines, P/WT-GIST often go undiagnosed or misdiagnosed because of their vague indolent symptoms.[7] Moreover, because many patients have potentially long lifespans and often live for decades with this background malignancy, the focus for surgical management shifts from an absolute cure to chronic management of disease burden and the associated symptoms for prolonged event-free survival (EFS).[13]

Classification

The classification of P/WT-GIST arose because 85% of patients lacked the hallmark *KIT*/*PDGRA* mutations compared with only 10% to 15% in adult GIST.[14,15] Since then, genetic evaluation has continued to reveal further unique molecular signatures, particularly in succinate dehydrogenase (SDH).[16] This has linked P/WT-GIST to the GIST-related cancer syndromes Carney triad and Carney-Stratakis syndrome, and has even led to the proposal of a new molecular classification based on SDH status, which encompass SDH-competent, SDH-mutant, and SDH-epimutant.[17–20]

Clinical Features

In less than 15% of P/WT-GIST that are SDH-competent, tumor and patient demographic features overlap with *KIT*/*PDGRA*-positive adult GIST tumors and should be treated according to adult guidelines.[13,20–22]

However, pediatric reports of GIST encompassing SDH-mutant and epimutants show unique clinical presentations compared with adults. Patients were overwhelmingly female, with a median age of 13 years old.[20,23] Because their lesions were 90% gastric in origin showing epithelioid or mixed histology, common presentations included anemia, epigastric pain, or gastric-specific symptoms.[24,25] Most significantly, patients presented with multifocal tumors and metastasis, especially to the lymph nodes in 45% of cases.[13] Additionally, multiple recurrences were common with 27%, 76%, and 84% of patients experiencing recurrence over 1, 5, and 10 years

after diagnosis, respectively.[26] Despite this, because of the indolent nature of neoplastic progression, patients with P/WT-GIST have a prolonged survival with few patients succumbing to their disease and a 16-year survival after diagnosis.[22,27]

Imaging, Diagnosis, and Staging

In adults, computed tomography (CT) is the gold standard for initial investigation and monitoring of treatment response.[9,10,28] However, because of the young age of patients with P/WT-GIST and their need for lifelong screening (discussed later), it is important to minimize radiation exposure. As a result, alterative imaging, such as MRI and contrast-enhancing ultrasound, are preferred.[29] In fact, these same imaging principles are adopted for the staging work-up, with the inclusion of thorough investigations for lymph node, liver, and peritoneum seeding because of frequent metastasis at presentation (**Fig. 1**).[29]

However, diagnosis is still established through histologic analysis and immunohistochemical staining of tumor specimens.[9,10] Endoscopic ultrasound–guided fine-needle aspirate for masses larger than 1 cm is highly recommended because it yields a diagnostic rate of 62% to 93%.[30,31] On the contrary, traditional endoscopic forceps are discouraged because of the poor diagnostic rates and associated bleeding complications.[32–34] Percutaneous image-guided biopsy should also be avoided and only adopted on a case-by-case basis because of the risk of tumor spillage.[10] This must be approached with extreme caution because spillage is significantly associated with recurrence in P/WT-GIST.[35,36] For this reason, if endoscopic ultrasound–guided fine-needle aspirate is not feasible, it may be prudent to conduct a primary surgical resection for pathologic diagnosis.[9,10]

Surgical Management

Currently, guidelines for the management and treatment of P/WT-GIST are based on case reports and limited series because data supporting consensus guidelines for P/

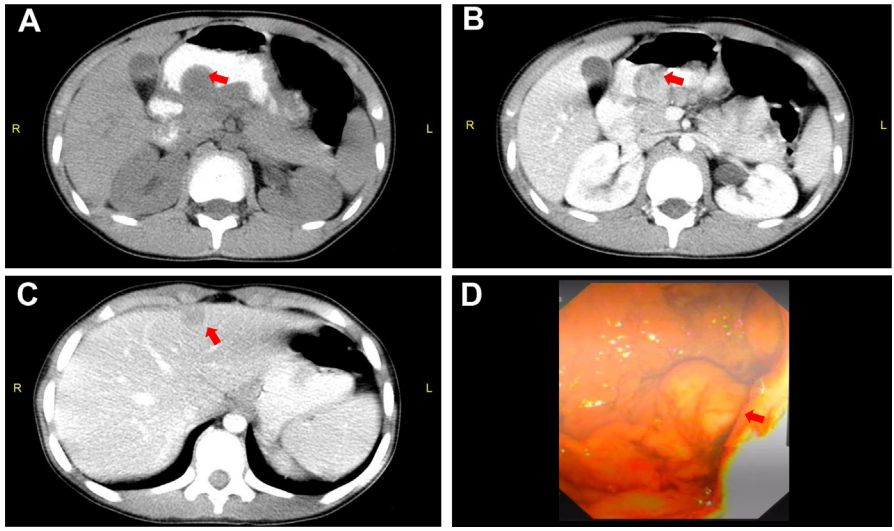

Fig. 1. A 12-year-old girl with abdominal pain diagnosed with multiple gastric tumors with lymph node metastases and a single liver metastasis. (*A*) Tumor and lymph nodes metastases (*red arrow*). (*B*) Tumor and lymph nodes metastases (*red arrow*). (*C*) Liver metastases (*red arrow*). (*D*) Tumor mass visualized during gastroscopy (*red arrow*).

W-GIST are lacking. However, surgical resection remains the mainstay treatment of all GIST including P/WT-GIST.[7,9,10,26]

Generally, a laparoscopic approach is adopted in lesions with favorable anatomic locations between 2 and 5 cm in size.[37] However, if these principles are adopted, tumor pseudocapsule must be preserved and resection specimens must be removed using a plastic bag to prevent spillage and port site seeding.[8] Additionally, if tumors run the risk of intraoperative rupture, especially in larger lesions greater than 5 cm, laparoscopic approach is strongly discouraged and open surgery should be considered instead.[10]

In adult GIST, complete R0 en bloc surgical resection for localized nonmetastatic tumors is the gold standard treatment and is achieved in 85% of patients.[38] Because GIST has the potential to occur anywhere along the gastrointestinal tract, surgical interventions are often site-dependent and are outlined in the latest guidelines (**Table 1**).[10] These are selectively applied to P/WT-GIST with the addition of sampling and possible dissection of lymph node draining basins and enlarged nodes because of frequent metastasis. In addition, surgical principles for P/WT-GIST are aimed at organ-sparing resection of primary tumor.[39] In P/WT-GIST, tumors are predominantly found in the stomach and usually occur in the antrum or lesser curvature.[38] As such, current literature focuses on gastric interventions.

Laparoscopic wedge resection has been adopted globally as the principle procedure for gastric GIST. However, a major difficulty with this approach lies in determining the appropriate resection margin often resulting in excessive gastric resection.[40] Additionally, certain tumor locations and morphology make laparoscopic wedge resection challenging especially when located close to the gastroesophageal junction (GOJ) or pyloric ring. This potentially results in partial gastrectomy being adopted instead because of risk of strictures and stenosis.[41] Despite this, no defined strategy exists to guide surgeons on selection of the appropriate resection technique. However, case reports and studies have independently outline various techniques based on tumor location and size.

Laparoscopic endoscopic cooperative surgery allows for a standardized gastric submucosal tumor resection independent of tumor location and site.[42] In this technique, endoscopic submucosal resection is performed around the tumor, which is followed by laparoscopic seromuscular dissection and tumor removal. Because tumor lesions are removed intra-abdominally, this procedure is limited to submucosal tumors without ulceration and bleeding. Unfortunately, laparoscopic endoscopic

Table 1
Surgical guidelines for localized GIST in adults

Site of GIST	Surgical Intervention
Esophageal	Resection Enucleation
Gastric	Wedge resection Segmental resection Partial/total gastrectomy (rarely indicated)
Duodenal	Wedge resection
Intestinal	Segmental resection
Colorectal	Segmental resection Local transanal excision (for small lesions)[a]

[a] Conduct sphincter-sparing approach wherever possible.

cooperative surgery has a higher risk of tumor rupture and peritoneal seeding because of tumor manipulation during surgery. As a result, other techniques, such as nonexposed endoscopic wall inversion surgery (NEWS), are ideal for intraluminal lesions because resection is conducted without exposure to the peritoneal cavity.[43] NEWS is an laparoscopic endoscopic cooperative surgery–related procedure and involves intraluminal submucosal incision on the laparoscopic side. Then, a spacer is used to push the tumor into the gastric lumen, allowing it to be excised endoscopically into the stomach and removed transorally. However, NEWS is not suitable for tumors of more than 3 cm, or those close to the GOJ or pyloric ring. These limitations are similar to endoluminal endoscopic full-thickness resection (EFTR) microsurgery, which has also been outlined in adult patients with GIST originating from the muscularis propria.[44] EFTR involves endoscopically precutting the surrounding mucosa and submucosa to expose the tumor. Then, dissection of the muscularis propria around the tumor is performed, followed by dissection of the serous membrane. If patients are eligible, this technique could be highly successful because a study has demonstrated promising results, achieving a complete resection rate of 100% with 0% recurrence after 1 year.

To overcome the limitations of NEWS and EFTR, laparoscopic wedge resection with the serosal and muscular layers incision technique is adopted.[45] In this novel technique, incisions are made into the serosal and muscular layers around the tumor laparoscopically. After the circumference of the tumor is excised, the tumor appearance shifts from intraluminal to extraluminal where a wedge resection is performed for its removal. This technique is optimal for challenging lesions located close to the GOJ or pyloric ring. Most advantageously, serosal and muscular layers incision technique does not require endoscopic submucosal dissection expertise and devices. Because it also does not require full-thickness gastric perforation as the mucosal and submucosal layers are left intact, the risk of tumor seeding is also prevented.

Postsurgical Outcomes

It is generally accepted that complete resection without tumor rupture is successful in halting disease progression. However, Weldon and colleagues[26] have demonstrated that EFS in P/WT-GIST is significantly more closely related to tumor biology compared with surgical factors, such as resection margins. Although reoperation is generally a common consideration with metastasis and recurrence, this might not be indicated for P/WT-GIST because subsequent resections were significantly associated with decreased postoperative EFS. National Comprehensive Cancer Network guidelines also outline that reresection is generally not indicated for microscopically positive margins, even in adult GIST.[8]

Although this might be concerning especially because disease progression and recurrence are common in P/WT-GIST, patients are afforded low mortality rates of less than 10%.[46] For this reason, P/WT-GIST must be considered in the paradigm of chronic disease with long-term management focusing on disease control, symptom management, and preserving quality of life. Therefore, indications for aggressive or repeat resections and their associated long-term sequelae must be critically evaluated against the potential benefit.

Novel Therapies and Follow-Up

Contrary to the immensely successful conventional tyrosine kinase inhibitor therapy adopted in adult GIST, P/WT-GIST continue to show nonresponse, inability to improve recurrence-free survival, and is associated with dedifferentiation.[39,47] Thankfully,

various therapeutic agents are being trialed and may have a promising application in P/WT-GIST.[48–50]

Considering the limitations of medical therapy and nature of the disease, cure is not likely. Thus it is imperative that patients with P/WT-GIST be monitored and surveilled frequently and consistently with lifelong follow-up to ensure the long-term survival of these young patients.[29]

NEUROENDOCRINE TUMORS IN CHILDREN

NET originate from neuroendocrine cells present in almost every organ in the human body. Their characteristic features and immunoprofiles allow them to be classified into one group regardless of their anatomic location. Similar to P/WT-GIST, most available data are not specific to the pediatric population because of its extreme rarity. The incidence rate of NET between 0 and 29 years of age is estimated at approximately 2.8 cases per million.[51] NET incidence in children varies between 0.1 (ovary, thyroid gland, cervix, foregut) and 0.6 (lungs) per million population. Moreover, only 5% to 10% of pediatric pancreatic tumors with incidence of only 0.018/100,000 in the United States are found to be NET.[52] Ninety percent of pediatric NET are benign and mainly solitary. They originate from pancreatic islet cells with insulinomas and gastrinomas being most common; somatostatinomas and VIPomas are exceedingly rare in children.[53]

Pediatric NET show gender and genetic predispositions. NET are observed more frequently in females, with appendix NET and pediatric bronchial carcinoid tumors showing female preponderance.[54–56] Multiple endocrine neoplasia type 1 (MEN1) and von Hippel-Lindau disease are the most frequent hereditary predispositions.[57] Other syndromes include: neurofibromatosis type 1, tuberous sclerosis, Lynch syndrome, and familial adenomatous polyposis.[58] In particular, pancreatic NET, especially gastrinomas, seem to be associated with genetic syndromes, such as MEN1. Therefore, genetic predisposition should be suspected when multiple primary tumors are present or specific clinical features are noticed.[59]

Classification

NET are widely distributed throughout the body. Hence, most of the clinical features are unique to the site of the origin and/or hormone overexcretion. The World Health Organization proposed a new diagnostic system based on results from various studies. This has significantly changed the diagnostic processes and treatment approaches in NET (**Table 2**).[60,61]

Clinical Features

Although most NET are initially asymptomatic, patient symptoms strongly correlate with tumor localization, its size, and hormonal secretion.[62] In adults, the most common sites are small intestine, rectum, and lungs.[63] This is in contrast to children and young adults, with the most common sites being the lungs and appendix.[64]

Bronchial carcinoids usually have an endobronchial location causing persistent cough, wheezing, shortness of breath, hemoptysis, or chest pain. As such, they are frequently misdiagnosed as benign conditions. Unlike adults, children are almost always symptomatic, with the most common presentation being obstructive pneumonia and recurrent pulmonary infections.[65]

In pediatric patients, NET of the appendix is usually found incidentally but can often present with symptoms of acute appendicitis in 63% to 75% of cases.[66,67] Despite this, appendiceal NET is only responsible for about 0.16% to 2.3% of appendectomies.[68]

Table 2
NEN 2018 WHO classification of selected NEN by site, category, family, and tumor type[14]

Site	Category	Family	Type	Grade	Current Terminology
Lung	NEN	NET	Pulmonary NET	G1	Carcinoid
				G2	Atypical carcinoid
		NEC	Small cell lung carcinoma (pulmonary NEC, small cell type)		Small cell lung carcinoma
			Pulmonary NEC, large cell type		Large cell NE carcinoma
Uterus (corpus and cervix)	NEN	NET	Uterine NET	G1	Carcinoid
				G2	Atypical carcinoid
				G3	Atypical carcinoid
		NEC	Uterine NEC, small cell type		Small cell carcinoma
			Uterine NEC, large cell type		Large cell NE carcinoma
Pancreas	NEN	NET	Pancreatic NET	G1	PanNET G1
				G2	PanNET G2
				G3	PanNET G3
		NEC	Pancreatic NEC, small cell type		Small cell NE carcinoma
			Pancreatic NET, large cell type		Large cell NE carcinoma

Abbreviations: NEC, neuroendocrine carcinoma; NEN, neuroendocrine neoplasm; WHO, World Health Organization.

Data from Hirota S, Isozaki K, Moriyama Y, et al. Gain-of-Function Mutations of c-kit in Human Gastrointestinal Stromal Tumors. Science. 1997;279.

Pancreatic NET are usually associated with abdominal mass, pain, and vomiting. Various hormonal symptoms are associated with pancreatic NET, such as hypoglycemia ± seizures in insulinoma, peptic ulcers in gastrinoma, or diarrhea in VIPoma.[58] Carcinoid syndrome is an extremely rare presentation of NET in children, in contrast to 0.7% of adults at presentation.[56] In around 60% of patients, NET secreting vasoactive substances involve the heart and cause carcinoid heart disease, resulting in right heart failure.[69]

Imaging, Diagnosis, and Staging

CT, MRI, PET, somatostatin receptor imaging, and hybrid PET/CT or PET/MRI are used to localize, grade, stage, and classify NET (**Fig. 2**). Contrast-enhanced CT is highly accurate for neoplasms larger than 2 cm, with a broad sensitivity range of 63% to 82%.[70] Because of better soft tissue contrast, MRI better visualizes some NET tumors with sensitivity and specificity of 93% and 88% in pediatric NET, respectively.[71] In MRI, pancreatic insulinomas and gastrinomas reveal T1 and T2 prolongation.[72] Somatostatin receptor imaging with radiolabeled somatostatin analogue octreotide (OctreoScan) is especially useful for visualization of gastrinomas, glucagonomas, and VIPomas with sensitivity between 75% and 100%.[73]

Recently, a new somatostatin analogue 68Ga-DOTA-tyrosine3-octreotide (DOTA-TOC) PET/CT has shown a higher detection rate and is an excellent tracer for and planning of NET patient management.[74] Its low toxicity, low radiation exposure, fast administration, and clearance time make it the most reliable diagnostic modality for

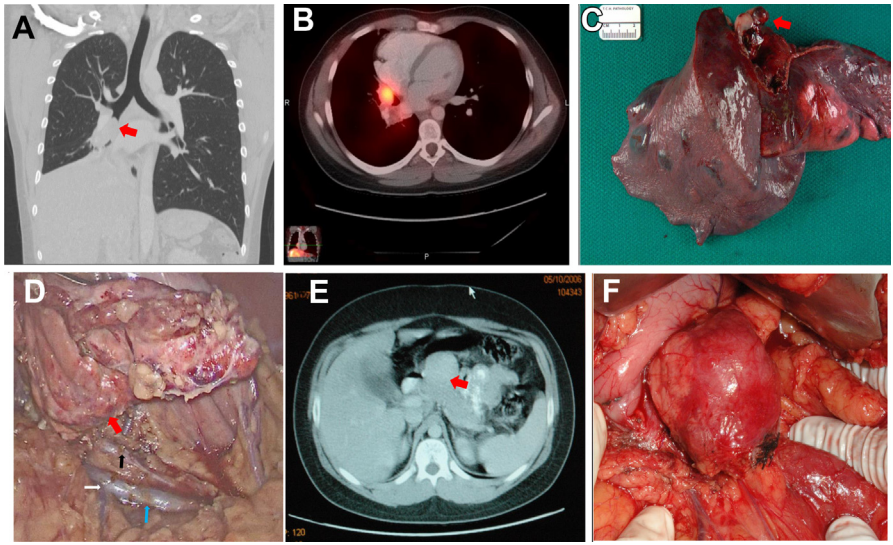

Fig. 2. (*A*) A 16-year-old boy with cough and Right Lower Lobe (RLL) collapse secondary to Right Medial Lobe (RML)/RLL endobronchial mass (*red arrow*). (*B*) Octreotide scan shows positive uptake within the mass. (*C*) Patient underwent thoracotomy with RML/RLL lobectomy with endobronchial carcinoid seen extruding from opened bronchus (*red arrow*). (*D*) An 8-year-old boy with hypoglycemia episodes found to have an insulin-secreting tumor in the body/tail of the pancreas distal to the inferior mesenteric vein (IMV) junction with the splenic vein (SV); laparoscopic splenic-sparing distal pancreatectomy performed with mass (*red arrow*) elevated off of the SV (*blue arrow*) and splenic artery (*black arrow*) and dissection taken to the IMV/SV junction (*white arrow*). (*E*) A 10-year-old boy with chronic constipation, diagnosed with pancreatic NET of head of pancreas; tumor mass (*red arrow*). (*F*) No metastases presented, and patient underwent central pancreatectomy.

the pediatric population. Thus, 68Ga-DOTATATE PET/CT should be adopted as the first-line diagnostic tool.

Although pathologic diagnosis is crucial for the treatment selection and prediction of the prognosis and the risk of progression, noninvasive laboratory tests can also be used in NET detection and follow-up. Serum chromogranin A is the most effective marker, with high levels strongly correlating with NET presence, especially in low-grade NET.[75] Additionally, higher serum levels of pancreastatin are also associated with poor prognosis, and is able to distinguish patients at high risk of recurrence.[76] Another useful marker in diagnosis and therapy monitoring is 5-hydroxyindoleacetic acid, showing specificity of up to 100%.[77] Other NET tumor markers described in the literature include: serotonin, neurokinin A, N-terminal pro–B-type natriuretic peptide, and neurone-specific enolase.[78]

Surgical Management and Postsurgical Outcomes

Because of the good long-term results, surgical management of pediatric NET is considered the first-line therapy for local-stage disease and is site-dependent.[79]

For appendiceal NET, various surgical interventions are described. Of the 0.3% of appendectomies confirmed at NET, 38% of patients underwent an ileocolic resection or right hemicolectomy.[80] The indications for more aggressive treatment included larger tumor size, extended invasiveness, and presence of tumor at resection margin.

Because some consider appendicectomy alone to be the most adequate treatment in children irrespective of NET size, lymph nodes involvement, tumor limited to the appendix, or mesenteric involvement, the need for a secondary colectomy is in question.[81] Others also suggest that simple appendectomy is only sufficient for tumors less than 1 cm or 1.6 cm, and right hemicolectomy should be recommended otherwise.[82] The North American Neuroendocrine Society reports that the 5-year mortality from appendiceal NET reached 29.5% for tumors 2 cm or greater. Thus, right hemicolectomy is recommended in those cases.[83] Additionally, although the "2-cm rule" is not applicable to adult duodenal, small bowel, and rectal tumors, which are often metastatic at smaller sizes, this is debatable in children.[84]

Pancreatic NET are extremely rare in children, hence data related to surgical management in this group are limited. Although surgery remains the crucial treatment, controversy still exists. Tumors less than 2 cm of size and those that are nonfunctioning are often considered to be left under observation because only 6% of them are confirmed to be malignant.[85] Because pediatric NET can localize in any part of the pancreas, surgical approach depends once again on tumor location.[86] The gold standard for surgical treatment of pancreatic head NET in adults and children is pancreaticoduodenectomy (Whipple procedure), with pylorus preservation (Traverso-Longmire modification).[52,87] In more distally located tumors, open or laparoscopic resection using distal pancreatomy, central pancreatectomy, or even tumor excision is applied.[58] Intraoperative ultrasound is helpful because some tumors tend to be multifocal. Complications, such as pancreatic leak, pancreatic deficiencies, and delayed gastric emptying, must also be avoided in pancreatic resections because they are associated with significant morbidity.[52]

Surgical treatment of pediatric bronchial carcinoid tumors is less controversial. Conservative procedures are the treatment of choice, because they are performed successfully by experienced thoracic surgeons. If possible, lung-sparing resections, such as sleeve resections or bronchoplasties, should be performed because the oncologic result is similar to pneumonectomy and offers a better quality of life.[88] In the pediatric population typical carcinoid tumors have a favorable prognosis following definitive surgical resection.[56]

Novel Therapies and Follow-Up

Unfortunately, surgical intervention in metastatic NET is not sufficient. Therefore, the main nonsurgical treatment options include somatostatin analogues, molecularly targeted therapies, cytotoxic therapies, and peptide receptor radionuclide therapy (PRRT). Increased expression of somatostatin receptors in NET tumors leads to targeted therapy with somatostatin analogues, such as octreotide and lanreotide.[89] They have shown an antitumor effect with regards to tumor progression and overall survival, especially in patients with metastatic midgut carcinoid tumors.[90]

Standard cytotoxic chemotherapy is believed to have limited benefits in metastatic NET. However, these may still be selectively effective. Temozolomide is an effective agent in the pediatric population with recurrent medulloblastoma/primitive neuroectodermal tumor.[91] Additionally, the combination of capecitabine and temozolomide was also shown to be effective in patients with grade 3 NET.[92] PRRT is another form of molecular targeted therapy approved as the standard of care treatment in progressive midgut NET. Good response of PRRT with 90Y and 177LU DOTA conjugated somatostatin analogues was reported.[93]

Although pediatric NET are rare, they do occur and may be associated with significant morbidity. Most patients are successfully treated with surgical tumor excision and no further management other than follow-up is required. Long-term follow-up is

strongly recommended, especially in bronchial NET because of their frequent recurrences.[94] Despite this, the definition of adequate follow-up for NET is still not clear. However, most papers suggest a complex frequent follow-up in the first 3 to 5 years after resection.[95] For carcinoids that are less than 2 cm and localized to the appendix, no further follow-up is required after appendectomy.[55] Because of proven genetic predisposition of NET more frequent screening is indicated in cases of genetic syndromes MEN-1, von Hippel-Lindau disease, tuberous sclerosis, or familial adenomatous polyposis. Even still, the 5-year overall survival in NET remains in the range of 78%, with NET localized in the colon/rectum, appendix, and thyroid tumor locations having an even better 5-year overall survival of greater than 95%.[96]

SUMMARY AND FUTURE WORK

P/WT-GIST and pediatric NET are extremely rare malignancies that show uniquely distinct clinical features from their adult counterparts. Although surgery is adopted in both malignancies as the mainstay treatment, the wide range of site-dependent presentations and lack of pediatric-specific consensus treatment protocols makes it challenging to identify the most efficient surgical approach. As a result, international cooperation to develop standardized pediatric-specific guidelines is urgently warranted in the future. This will optimize the outcome and quality of life for these young patients.

CLINICS CARE POINTS

- Surgical management of pediatric GIST is the mainstay as medical treatments continue to show non-response and are associated with increased complications.
- Repeat resections for pediatric GIST recurrence is often not indicated as they are significantly associated with decreased postoperative EFS.
- Pediatric NET are associated with gender and genetic predispositions such as multiple endocrine neoplasia type 1 and von Hippel-Lindau disease.
- Surgical manegement of pediatric NET is considered first-line therapy and is largely site-dependent.

DISCLOSURE

The authors declare no commercial or financial conflict of interest.

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