Schwannomas of Gastrointestinal Tract; a comprehensive review

Heng Siang Ting, BM Yashodhara, Htoo Htoo Kyaw Soe, Uduman Ali Mohamed Yousuf, Jaswant Singh

ABSTRACT

Gastrointestinal Schwannomas (GIS) are neurogenic, spindle cell, mesenchymal tumors, and arise from Schwann cells of myenteric plexus; the cells which form the sheath of the nerves. Schwannomas (SNs) usually arise from spinal roots and peripheral nerves in Schwannomatosis, the third major form of neurofibromatosis, but they are most well-known to originate from cranial nerves as in vestibular schwannomas. On the contrary, a sporadic Schwannaoma which occurs in hollow organs such as the GI tract is remarkably rare. The Gastrointestinal Schwannomas pose a diagnostic & interventional challenge as it is difficult to differentiate them, peri-operatively or pre-operatively, from more commonly occurring, more malignant, Gastrointestinal-Stromal Tumors (GIST). The exact incidence of gastrointestinal Schwannomas is not known, due to lack of consensus in the nomenclature of these tumors; they are called schwannomas, neurinomas, neurilemmomas, neurolemmomas, and Schwann cell tumors. The literature review suggests that they contribute to 1% gastrointestinal tumors and 2–8% of gastrointestinal mesenchymal tumors.

Keywords: Comprehensive review, Gastrointestinal schwannomas, Gastrointestinal-Stromal tumors, Gastrointestinal tract, Schwannoma

INTRODUCTION

The most common tumors of the gastrointestinal (GI) tract are epithelial neoplasia and lymphomas. Each of the intricate & complex mesenchymal tissue of gastrointestinal tract has the propensity of differentiating into a variety of tumoral lesions, and these are now called Mesenchymal (non-epithelial, stromal) non-gastrointestinal stromal tumors (Non-GIST) of the digestive tract (MNGTDT) after decades of confusions about their nomenclature [1].

There were times when naming these tumors were non-uniform and this created enormous confusions and controversies in defining the histogenesis, pathogenesis, anatomical and clinical features, biological behaviour, pathology, classification, and risk stratification, and particularly the management of these pathologies. Assisted by local & conventional, transcontinental, limited

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Schwannomas were first described by Verocay in 1910 [2]. Schwannomas are benign, slow-growing mesenchymal neoplasms and originate from Schwann cells. They are rare tumors, occurring most commonly in acoustic nerves or spinal nerves [3]. The exact incidence of GI schwannomas (SNs) is not known. Review of the literature suggests that soft tissue tumors contribute about 1% of all gastrointestinal tumors; and schwannomas account for about 2% to 8% of all gastrointestinal submucosal tumors [4–7]. The common mesenchymal tumors of GIT are mentioned in Table 1.

Schwannomas are frequently benign, slow-growing tumors that originate from the sheath of peripheral nerve fibers within mesenchymal tissue. They are typically asymptomatic and can be found incidentally during imaging or endoscopic evaluation. Schwannomas are classified into two main subtypes: sporadic and neurofibromatosis-associated. The latter is seen in patients with Neurofibromatosis Type 1 (NF-1) and Neurofibromatosis Type 2 (NF-2). Schwannomas in NF-1 are usually multiple and occur in various locations, while those in NF-2 are more localized and often involve the head and neck region.

<table>
<thead>
<tr>
<th>GI Schwannoma (GIS)</th>
<th>Soft Tissue Schwannoma</th>
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<tbody>
<tr>
<td>Prominent lymphoid cuff</td>
<td>No lymphoid cuff</td>
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<tr>
<td>[1, 4, 11, 12, 13]</td>
<td>Encapsulated</td>
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<tr>
<td>Non-encapsulated, well circumcised [1]</td>
<td></td>
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<tr>
<td>Vague palisading at most, Bipolar spindle cells, cells with pointed ends, [4]</td>
<td>Prominent palisading and Verocay bodies, absence Antony A and Antony B areas</td>
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<tr>
<td>Absence Antony A and Antony B areas [13]</td>
<td></td>
</tr>
<tr>
<td>Lacks hyalinised vessels</td>
<td>Frequent hyalinised vessels</td>
</tr>
<tr>
<td>Lacks xanthoma cells</td>
<td>Frequent xanthoma cells</td>
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<tr>
<td>No NF2 mutations</td>
<td>40-60% have NF2 mutations</td>
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</table>

Table 1: The common mesenchymal tumors of GIT

<table>
<thead>
<tr>
<th>Gastrointestinal Stromal Tumors (GIST)</th>
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<tbody>
<tr>
<td>Lipomas,</td>
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<td>Leiomyomas,</td>
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<tr>
<td>Leiomyosarcomas,</td>
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<td>Fibromas,</td>
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<tr>
<td>Desmoid Tumors</td>
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<tr>
<td>Schwannomas</td>
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247 B.C. [14, 15]. Neuramas of NF-1 were first discovered by Friedrich Daniel von Recklinghausen in 1882, and he was the first to describe the source of these skin tumors to be nerves and he also coined the name of the disease, neurofibromatosis also called as von Recklinghausen’s disease [14, 15]. Table 3 gives a brief summary of important historical details of neurofibromas and schwannomas, their first nomenclature and syndromic descriptions over the last century.

**Do GI Schwannomas occur in NF-1, NF-2 and Schwannomatosis (NF-3)?**

Occurrence of NF-1 is more common than NF-2 and constitutes 97% all cases neurofibromatosis and has an incidence of 1 in 3500 live births, NF-2 (2–3%) has an incidence of 1 in 25,000 live births. NF-1 and NF-2 are genetic syndromes, with autosomal dominant mode of inheritance, that lead to tumorous conditions in the body and further evaluation should be based on the symptoms of the patients; if they have bone symptoms the evaluation should focus on osteosarcomas, GI symptoms necessitate investigations for periampullary & duodenal tumors (GIST tumors, stomatostatinomas). Leimyosarcomas occur less frequently in these conditions. In NF-2 common tumors are bilateral acoustic schwannomas and meningiomas of brain [9].

Davis and Beck estimated that gastrointestinal involvement occurs in 25% patients with NF-1 [16–18] commonly in jejunum or ileum [16] and in a series analysis of all articles on NF-1 and NF-2 in PubMed & Medline, it was found that, histologically these tumors commonly are carcinoids (41%), Neurofibromas (30%), Neurfibrosarcomas (8%) and a GI adenocarcinomas (8%) or even GISTs [9]. Malignant transformation of GI tumors in NF-1 patients is higher than in the general population and is estimated to be 2–5% [19]. GI Schwannomas occur rarely in NF-2 but not reported in NF-3 [9, 20]. The other genetic syndrome associated with GI Schwannomas is Carney’s complex [2]. On review of available literature, sporadic cases of GI Schwannoma and unilateral vestibular schwannoma have been reported; the patent had intussusception as the presenting symptom due to GI schwannoma in descending colon and it occurred many years after a surgical removal of unilateral Vestibular Schwannoma [7] Apart from NF-1 and NF-2, a third distinct genetic syndrome has been identified called as Schwannomatosis (NF-3) which is very rare and is characterized by multiple schwannomas without the common presentations of NF-1 and NF-2 [21]. The schwannomas in these patients are distributed in cranial, spinal and peripheral nerves but vestibular schwannomas are not seen like in NF-2 [21]. There are a few varied criteria for making the diagnosis of NF-3 but the one which is easy to follow is that any patient older than 30 years with two or more non-intradermal schwannomas and who has no vestibular schwannomas on MRI Contrast and lacks genetic mutations of NF-2, and has a first degree relative (s) with confirmed Schwannomatosis, is diagnosed have NF-3 [21].

**GI Schwannomas (GIS)**

Since Verocay first described Schwannomas in 1910, [4, 22] and Daimaru first reported GIS in 1988, [4] they are increasingly being diagnosed with the recent advances in diagnostic technology and immunohistochemistry [4, 22]. They do occur sporadically but not that commonly with NPs [20, 22, 23]. These tumors can arise in any part of the GI tract from esophagus to colon and rectum, [4, 11, 17] and rarely in the small intestine [17, 24, 25]. 70% GIS occur in the stomach [20]. These slow growing soft tissue, spindle cell tumors constitute 1% of GI tumors, [4, 22] 0.2% of all gastric tumors, [13, 17] and 2–8% of GI mesenchymal tumors [4, 13, 22–25]. In comparison, the most common, the other GI spindle cell mesenchymal tumor GIST, occurs 50–100 times more commonly than GIS [11] and constitutes 80% GI mesenchymal tumors [13] Albeit both these spindle cell mesenchymal tumors may have similar clinical presentation and features of resemblance on endoscopy or colonoscopy, they need to be differentiated early from each other pre, peri or postoperatively as they run altogether different course in connection with complications, treatment and prognosis with GIST tumors being more malignant than GIS. Only a few case reports on a review of the literature [26, 27] mention malignant nature of GIS; 8 in GI hollow visera, 4 in pancreas [27] and a few in the small intestine [19, 25, 28, 29].

**Presentation of GI Schwannomas**


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**Table 3:** Gives a brief summary of important Historical details of Neurofibromas and Schwannomas, their first nomenclature and syndromic descriptions over the last century [14, 15]

- **Robert William Smith** in 1849: The first systematic review on these NF tumors:
- **Van der Hoeve (1921), Yakovlev and Guthrie (1931), and Van Bogaert (1935):** described the skin features of NF-1 as neurocutaneous syndromes and phacomatosis.
- **Eduard Sandifort in 1777 AD:** The first known mention of an acoustic neuroma
- **John H. Wishart:** gave the first account of bilateral acoustic neuroma in 1822; after an autopsy, on a 21 year old dead man who had the disease from his childhood.
- **Older, Virchow, von Recklinghausen, and Verocay:** first classified “neuramas”
- **Masson & Penfield:** first used the word: “schwannoma”.
- **In 1903 Henneberg and Koch:** described: NF2 in detail.
- **Young, Eldridge, and Gardner:** in the late ’70: established NF2 as a distinct familial entity.
Other symptoms also depend on the location of these tumors in GI. Schwannomas in esophagus [13, 24, 32] can present with dysphagia [7, 9] and those originating from small intestine can present with fatigue, anemia, [8] intussusception, and mass abdomen [9, 13, 33]. Sometimes these tumors are picked up coincidentally [32] during routine endoscopic screening [34] or by endoscopic evaluations prompted by changes in bowel habits, abdominal pain, [13] GI bleeding, [4, 13, 14] difficulty in defecation [1, 9] or positive occult blood tests performed during colorectal screening [23, 35]. When they occur in stomach, the commonest site of these tumors, they are usually asymptomatic [36, 37] and in the subset of symptomatic patients, presentation due to bleeding as the first symptom is seen in 14% cases; and this usually in the form of melena and rarely as hematemesis [36]. Other presentations of GIS in stomach, include epigastric pain persisting for many months, [37] vomiting, weight loss, perforation, with abscess formation, and rarely pleural effusion [13]. The presentation of malignant GIS is similar to non-malignant GIS [19].

Age of Presentation of GI Schwannomas

Unlike the Vestibular intra-cranial schwannomas in NF-2 which present in early childhood or late adolescence, [38] age of occurrence of GIS varies from 18–87 years, but commonly in 6th to 7th decade of life [39] and equal in incidence in both genders, [4, 22, 26] however some of the literature, reports a decade earlier [10, 17, 31] median-age of incidence GIS with a female preponderance [10, 13, 17]. Schwannomas vary in size from 0.5 cm with a median tumor-size of 52 mm, [31] to 15 cm in hollow visceral organs of GI, [1, 10, 36] while 2

Table 4: Differential Diagnosis of GI Schwannomas & their Immunohistochemistry [2, 10, 13, 20, 22, 27, 39, 42, 43]

<table>
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<tr>
<th>S-100</th>
<th>GIST</th>
<th>GANT</th>
<th>Neurofibromas</th>
<th>Ganglio-neuroma</th>
<th>Intestinal Perineurinoma</th>
<th>Leiomyoma</th>
<th>Leiomyoblastoma</th>
<th>Leiomyosarcoma</th>
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<td>Vimentin</td>
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<td>Neuron Specific Enolase</td>
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<td>C -KIT [2, 3, 44]</td>
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<td>PDGFRA [2, 44]</td>
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<td>DOG -1 Mutations [2, 44]</td>
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<td>PCNA</td>
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<td>Synaptophysin</td>
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<td>Chromogranin</td>
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<td>CD 68</td>
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<td>Actin, Cytokeratin</td>
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<td>Syndromic Associations</td>
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<td>NF -1</td>
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<td>NF -2</td>
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<td>NF -3</td>
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<td>Carney’s Complex</td>
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Platelet derived growth factor receptor alpha PDGFRA; Smooth Muscle Antigen (SMA); Proliferating Cell Nuclear Antigen (PCNA).
-4 cm in intracranial location, [38] 1.5 cm to 20 cm in pancreas [27]. The mass of the tumors varies from 1-2 gm to 3000 gm [1, 26]. Tumor size above 5 cm in GI tract is considered to be high risk for potential complications and hence needs a curative resection and if not resected, tendency to become malignant is high [29, 39].

**Investigations**

GI schwannomas are difficult to diagnose preoperatively, [7] although not impossible, [31] as radiological and endoscopic findings are non-specific, not pathognomonic and they masquerade as other common tumors of the bowel [10, 33]. A limited information about these tumors can be obtained by Endoscopic evaluations, CT Scans, MRI scans [13] and tumor markers [31, 33]. Histopathology of the resected specimen and aided by immunohistochemistry is the gold standard in the diagnosis of GI Schwannomas [40] GIS during the endoluminal examination appear as bulging masses due to their location in submucosa or muscularis propria [20] may resemble other submucosal lesions, but may be more hard, superficially ulcerated, [4, 13, 36, 40] solid or calcified; [4] Due to these characteristics it is difficult to biopsy these lesions & to obtain adequate tissue for histopathological diagnosis pre-operatively. EUS has a role in detecting these hypoechoic lesions- [13] with marginal halos & no internal echoes, [13]- as it identifies their layer of origin [13]. Moreover it also aids in directed biopsy which improves the chances of pre-operative diagnosis by 10%. Inaddition, EUS helps in the detection of irregular margins, surrounding lymph nodes, and cystic spaces in the lesion; the features suggesting malignant transformation [4]. GIS on Barium examination appears as a medium to large contrast deficit [13]. In CT scan and MRI images GIS appear as encapsulated lesions arising from the submucosa and look as homogeneous attenuated masses [4, 13, 26] before and after intravenous contrast [12, 13] a feature that can help differentiate them from GISTs which appear heterogeneous due to cystic changes, hemorrhage or necrosis [12, 13]. Due to their high avidity for fluorodeoxy D-glucose uptake on PET scan GIS faça de other malignant stromal tumors and hence PET scan is of little diagnostic value [4, 13]. Paradoxically, this peculiar behavior of GIS on PET scan could be used as a diagnostic tool and GIS should be suspected if a glowing submucosal lesion is picked up on PET scan [13]. SNs appear hypointense on T1-weighted MRI image and hyperintense on T2 weighted MRI image relative to the muscle [1, 12, 13, 27]. Once these sequence of investigations are done, surgical resection, histopathology and immunohistochemistry have to be done to confirm the diagnosis of GIS. The resected specimen appears well-circumcised, non-encapsulated, solitary, round or oval [1] yellowish-white lesions [22]. When subjected to histopathology, it typically shows rich cellular tissue consisting of spindle cells with palisading nuclei, [4, 11] and a lymphoid cuff [4]: Table 2, vide supra, mentions the commonly found histopathological features of GIS.

**Immunohistochemistry (IHC)**

Sarlomo-Rikala [41] and Christopher [41] were the pioneers who used immunohistochemistry to differentiate SNs from other GI mesenchymal tumors [41] Leiomyoma and Leiomyosarcomas which originate from the smooth muscle, muscularis mucosa and even the smooth muscle of small vessels digestive wall [1] are positive for desmin and smooth muscle actin; GISTs are positive for CD34, CD117 [41]. GIS is typically positive for S-100, [4, 13, 41] Vimentin [4, 41] and unlike peripheral soft-tissue SNs are positive for Glial Fibrillary Acidic Protein (GFAP); GIS is negative for C117, CD34, actsins, SMA, Desmin, c-KIT and Cytokeratins. [4, 13, 22] Table 4 [2, 10, 13, 20, 22, 27, 39, 42, 43, 44], mentions the immunohistochemistry features of GIS, GISTs and other tumors. Malignant GIS are positive for GFAP, Vimentin and Neuron specific enolase (NSE), CD68 and negative for CD117, CD 99, CD34, CD20, S-100, Desmin and SMA [19].

**Microscopy and the role of frozen section biopsy**

Schwannomas and GIST on routine microscopic examination show spindle cells. The GIS has prominent cuff [1, 4, 11–13]. The arrangement of the spindle cells in schwannomas is pathognomonic and is called a Verocoy body. The nuclei inside the cells in Schwannomas are slender and ovoid with pointed ends. The tip of the spindle cells have neurofibrillary elements. In hypercellular areas on Haematoxylin & Eosin (H&E) stains, spindle cells have palisading appearance due to alignment of nuclei of these spindle cells in a line or a row. The alternating patterns of palisading blue nuclei interspersed or stacked between pink neurofibrillary stroma, on microscopy in Hematoxylin and Eosin staining, are called Verocoy bodies; named after Verocoy, who first described these in schwannomas. The hypercellular areas of schwannomas with verocoy bodies on H&E are called Antony A areas, while Antony B areas have more diffuse arrangement of spindle cells with more stroma and myxoid tissue [4, 13], as detailed in Table 2.

The definitive diagnosis of Schwannomas is done by paraffin section which allows visualization of all the microscopic details, while frozen section only shows spindle cells [45] and hence, missing the other vital details as described above and so, it does not help in differentiating between GIST and Schwannoma [46].

**Treatment**

Size and location of these tumors and their relation to surrounding structures determine the type of operation [13]. Wedge resection, partial or subtotal gastrectomy, elective laparoscopic gastrectomy, [37]
could be done for SNs in stomach [13, 41]. Endoscopic resection [34], laparoscopic hemicolecotomy, [47] and endoscopic-laparoscopic resections, [36] Endoscopic mucosal resection (EMR) [34], are treatment options for tumors arising from other parts of GIT. Complete surgical resection with tumor-free margins is the curative treatment of choice for GI Schwannomas, in general, irrespective of their location [7, 37].

Malignant GIS is treated by all three accepted oncological interventions - surgically by resection, radiotherapy and chemotherapy—all applied together or individually and this decision is on an individual case basis [19].

**Prognosis**

These tumors are generally benign and slow growing and hence have an excellent prognosis [6, 13, 41]. In a case series of intra-abdominal Schwannomas, the patients were disease free for a year in one study [13] and asymptomatic for a median follow up of 22 months after the curative resection (range 1–120 months) in another study [31]. In case of malignant transformation, the response to chemotherapy and radiotherapy remains uncertain [7]. Unlike GI adenocarcinomas, these mesenchymal tumors, including GIST, have a lower tendency to metastases to regional lymph nodes or distant organs [13]. Malignant GIS have a poor prognosis as suggested by a series analysis showing that only 4 out 29 patients survived at five years [19].

**CONCLUSION**

GIS are not very common tumors and it is not easy to identify them, but in patients with syndromic presentations or in sporadic cases, the diagnosis could easily be made if EUS, PET scan, biopsy and IHC are utilized as tools to confirm the diagnosis.

**REFERENCES**


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Htoo Htoo Kyaw Soe – Substantial contributions to conception and design, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Uduman Ali Mohamed Yousuf – Substantial contributions to conception and design, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

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The corresponding author is the guarantor of submission.

Source of Support
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Consent Statement
Written informed consent was obtained from the patient for publication of this study.

Conflict of Interest
Authors declare no conflict of interest.

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