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REVIEW

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Review of the androgen receptors and gastrointestinal cancer

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Abstract

Gastrointestinal (GI) cancer is the prevalent cause of global cancer deaths, and its effective treatments are lacking. This common malignancy can be identified through hematomas or black stools. It includes the cancers of digestive system, *i.e.*, esophagus, stomach, liver, pancreas and colon. It is surgically removed followed by the conservative management. The incidence of GI cancer in men is 2–3 times higher compared to women. This higher prevalence in men is because of the involvement of sex steroid hormones via androgen receptor. The clinical case studies in men are continuously being conducted, however there are unanswered questions regarding the therapeutics. In this review, future therapeutic strategies of GI cancer and gastrointestinal stromal tumor (GIST) are being encompassed.

Keywords

Gastrointestinal cancer; Gastrointestinal stromal tumor; Sex steroid hormone; Men's health

1. Introduction

Gastrointestinal (GI) cancer has poor prognosis and is thus the leading cause of global deaths with no effective treatments [1]. Gastrointestinal stromal tumor (GIST) is the starting point of GI cancer and the most prevalent mesenchymal tumor of GI tract. It is often linked with bleeding, upper abdominal pain, and intestinal obstruction. It can be identified by hematoma or black stools and is the most common in stomach (55.6%) and least in esophagus (0.7%). The conservative management is required after its treatment [2]. GISTs are divided into tyrosine kinase (KIT)/platelet-derived growth factor receptor alpha (PDGFRA) variants and KIT/PDGFRA wild type (WT). WT GISTs are categorized as SDH-deficient and SDH (succinate dehydrogenase). GISTs range from centimeter-sized lesions to tumors. They arise in the digestive tract wall and extend inward toward the mucosa, into serosa, and in both directions. However, the necrosis or bleeding, or multiple tumors rather than single growth may predict malignancy [3]. GIST patients may suffer weight loss, vomiting, bloating, hypoglycemia, or low plasma glucose concentration. These tumors are treated by the surgical endoscopic resection. The pharmacological interventions include tyrosine kinase inhibitor imatinib (Gleevec) which targets c-KIT cluster of differentiation-117 (CD-117). The medical treatments include glucocorticoids, recombinant human chorionic gonadotropin (rHCG), and glucose-raising agents like glucagon [4]. Cancer being accepted as a disease is caused by the combination of genetic traits and environmental factors. The individual differences have key role in the underlying causes of GI cancers [5].

GI cancers include liver, stomach, esophageal, apocrine and colorectal cancers. They are rare cancers with low incidence, however, with higher frequency in men compared to women. This can be attributed to lifestyle patterns such as alcohol consumption, tobacco use, obesity and diabetes [6]. Hormones also effect the cancer development and treatment. The androgen receptor (AR) has important role in GI system. ARs are essential sex steroid receptors having key part in many cancers. It has pathological importance and thus employed as a drug in treating prostate cancer or as targeted therapeutic agent to inhibit the progression of female cancers like ovarian and breast, and to prevent tumors development, growth, or spread [7]. AR is expressed in several cell types and particularly in hormone-dependent cancers such as prostate and breast. AR is also found in stomach, bladder, lung, kidney, liver and pancreatic cancers which do not rely on the action of sex steroid hormones, and thus suggest a link between gender and cancer. AR expression is higher in men compared to women. The correlation between mortality and gender is established as a cancer risk factor. There is thus a need of studies on hormonal activation and cancer. Moreover, research is required on the AR role in cancer [8]. The sex steroid hormones in GI tract are linked to colorectal tissue, and in developing colorectal cancer (CRC). Furthermore, they regulate the synthesis of 17β-hydroxysteroids oestrone (E1) and oestradiol (E2), and sex hormones in colon and GI tract [9]. Sex hormonal factors corresponding to male prevalence of GI cancer include testosterone, dihydrotestosterone, androgen receptors, and deficiencies in DNA or nuclear proteins, or homeostasis-related functional proteins [10].

Cohort studies have shown gender difference in GISTs development, despite having no association with tumor size or

the metastases. The higher incidence in men is because of aggressive nature of male tumors and is biased by the longer life expectancy of women [11]. AR role in GI cancer and its correlation with GIST has increased the interest in GI cancer and GIST pathology which largely affects men. This review is aimed to discuss (1) AR and GI, (2) GIST expression and action mechanisms in men, (3) the causal relation between GI cancer and AR, and (4) future of the GI cancer prevention and treatment.

2. Androgen receptors and gastrointestinal cancer

Five types of GI cancers are esophageal, stomach, liver, pancreatic, and colorectal. Esophageal, stomach, and liver cancers are mostly found in Asia, while colon and pancreatic in Europe and North America. Preventive measures are important to control GISTs, which include tobacco and alcohol usage, obesity management, immunization against hepatitis B virus, and CRC screening [12]. In addition to primary and secondary preventions in controlling malignancies, biological sex differences are interpreted differently regarding immunity. Biological sex has an impact on inflammation. Inflammation and disease have stronger inflammatory response in women, which protects against the infection. Men have weaker inflammatory response and are more likely to die from infections [13]. GI cancer is associated with obesity, and the chronic inflammation caused by obesity increases the risk of GI cancers including pancreatic (cholecystitis), esophageal (esophagitis or Barrett's esophagus) and CRC (ulcerative colitis and Crohn's disease). Men are at higher risk with 1.86 to 4.52 folds increase in mortality. There is 1.46 to 2.76 folds increase in obese women [14]. Visceral obesity enhances gastroesophageal reflux to increase the Barrett's esophagus risk and the adenocarcinoma through independent mechanisms. Other mediators may also link obesity to the risk of esophageal adenocarcinoma. Among the adipocyte-derived mediators, increased leptin levels are associated with the progression to esophageal adenocarcinoma [15].

Esophageal cancer (EC) of GI tract is 9th common global cancer and 6th leading cause of cancer deaths. The prognosis, early diagnosis, and treatment are critical because of <20% five-year survival rate. EC is more prevalent in men, *i.e.*, 69% of cases which are 2.5 times higher than in women, as reported by Globocan 2020 [16]. EC is incurable. It starts in the esophageal wall and spreads outward through other layers like mucosa, submucosa, adenohypophysis, and adventitia. It is difficult to prognose and diagnose because of the lack of symptoms at earlier stages. Furthermore, more than half of the patients develop distant metastases in 5 years with high mortality rate [17]. Consolidation surgery in treating EC does not increase postoperative complications, however the history of diabetes, coronary or cardiac disease, carbon monoxide dispersion, and preoperative albemaie (ALB) are the independent risk factors [18].

Gastric cancer (GC) has the highest incidence rate, especially in East Asia, and thus high disease burden with high mortality. GC is prevalent in men with variety of etiologies. GC specificity requires an understanding of cancer prevention and management from pathological perspective [19]. In a study, GC was more prevalent in males with 726 out of 1039 patients (69.9%). Patients had mean age of 56.2 years with 5-year overall survival rates similar to the GC patients undergone laparoscopic treatment for lymphadenectomy [20]. A clinical trial of 152 male GC patients depicted relationship between muscle mass ratio (MMR) and total complications for predicting the complications after minimally invasive distal gastrectomy (MIDG) surgery in GC patients [21].

Liver cancer (LC) has been tripled since 1980s. The risk factors for LC include chronic infections (hepatitis B virus HBV, hepatitis C virus HCV), metabolic disorders like non-alcoholic fatty liver disease (NAFLD), type 2 diabetes (T2D), alcohol consumption, tobacco behavioral factors, and aflatoxins [22]. The two prevalent primary liver cancers (PLCs) in adults are hepatocellular carcinoma (HCC) and cholangiocarcinoma (CC). PLC risk is increased by the immunological, cellular, infectious, genetic, and molecular factors. Furthermore, the major factors in chronic liver disease (CLD) are diabetes, metabolic comorbidities and visceral fat [23].

Most cases of pancreatic cancer (PC) are sporadic. PC risk factors include gender, smoking, diabetes, alcohol consumption, and family history. The pathogenesis of PC is poorly understood. Some cases are detected at early stages, and germline variants are seen in high-risk patients. Above 5–10% PC patients carry mutations in ataxia telangiectasia mutated gene (ATM), breast cancer type 1 (BRCA1), BRCA2 and DNA mismatch repair genes (DNA MMR genes) mutL homolog 1 (MLH1), mutS homolog 2 (MSH2), MSH6 and PMS1 homolog 2, mismatch repair system component (PMS2) associated with Lynch syndrome (LS) [24]. The androgens have key role in PC growth and progression. AR antagonist enzalutamide is the first-line PC treatment along with gemcitabine and nab-paclitaxel. Its pharmacokinetic profile was evaluated in a clinical trial on 24 PC patients aged 68 years and above. AR-derived enzalutamide administration was safe regarding the toxicity and efficient in PC treatment [25].

Colorectal cancer (CRC) is the 3rd common cancer and 4th leading global death cause. This GI cancer has higher incidence in men aged 50–59 years. The sex steroid hormones can be responsible for CRC development. This development is different in males and females due to the effect of sex chromosomes, autosomes, and loss of X-inactive specific transcript (XIST) expression which can promote tumor development [26]. Food, nutrients, and beverage intake are important in CRC development. High-risk foods include red meat, processed meat, alcohol consumption, egg, sugary beverage, chocolate and candy. Healthier foods are milk, cheese, other dairy products, fruits, vegetables, whole grains, legumes, fish, green tea, coffee, chocolate and wine. These foods possess dietary fiber, fatty acids (omega-3, polyunsaturated fatty acids), calcium, polyphenols, curcumin, selenium, zinc, magnesium and vitamins A, C, D, E, B, B6, B9 and B2. There is a combination of micronutrients and multivitamins which reduce the incidence of recurrent adenomas [27]. Changes in gut microbiome may predict CRC development that varies by gender. Sexual dimorphism in microbiota is a CRC hallmark [28].

3. Androgen receptors and gastrointestinal signal

Hormones are the activating ligands for respective nuclear hormone receptor (NHR) proteins: the estrogen receptor (ER) in breast, ovarian, and endometrial tissue, and AR in prostate tissue. It is a potent activator of oncogenes to maintain hormonal signaling pathways despite the attempted blockade as a mechanism of disease progression [29] (Fig. 1). This induces AR phosphorylation at serine 81 (pARSER81)1-4, and androgen depletion in androgen deprivation therapy (ADT), which promotes cell proliferation and reduces cell death via AR activation [30]. AR is activated by the testosterone and 5α-dihydrotestosterone (DHT), and highly expressed in accessory sex organs, testes, breast, vagina, and cervical tissues or glands along with fat, muscle, and bone. AR expression is pronounced in hepatocytes. Sex-specific functions of AR are demonstrated in rats despite its widespread expression in digestive system, *i.e.*, mouth, GI tract and liver. Male rats develop hepatic steatosis and insulin resistance under high-fat feeding to indicate AR involvement in nutrient metabolism [31]. GI tract has several movement patterns for nutrients and waste in the body [32]. Neuregulin1 (NRG1) and its receptors are present in various parts of GI tract. They are detected in enteric nervous system (ENS), and mucosal and muscular layers of GI tract. NRG1/ErbB pathway regulates the ENS development and differentiation, and intestinal epithelial function. Dysregulation of this pathway may lead to range of gastrointestinal diseases [33]. These GI dysfunctions are referred to as the functional gastrointestinal disorders (FGIDs), or the disorders of gut-brain interaction (DGBI). The digestive health major problem relates to fewer symptoms whose distinction is not always clear [34].

ARs are expressed in GI tract which is the main site for biological processes [35]. AR is a sex steroid hormone used as prostate cancer pathology and as nuclear transcriptional regulator to mediate the growth stimulating effects of androgens [36]. AR positive expression is identified in prostate (87.8–100%), breast (34.3–94.9%), ovarian (48.7–97.1%), endometrial (53–61.1%), adenocarcinoma (70%), teratoma (60%), renal cell carcinoma (41.8–62.7%), bladder (43.2–48.7%), granular cell tumor (40.7%), leiomyoma (33.3%), GI stromal tumor (31.1%) and urothelial carcinoma of renal pelvis (30.4%), with the most prevalence in prostate, breast, and ovarian cancers [37]. An AR survey of GI organs, GISTs, and GI cancers can assist in understanding the action mechanism of AR and its genome. The recurrent increases in AR chronic atrophic gastritis (CAG) are associated with male CRC. AR gene may regulate vitamin D and its receptor oncogenesis [38]. AR is associated with cell signaling and eye-related pathways, antitumor drug resistance pathways, estimated glomerular filtration rate (EGFR) tyrosine kinase inhibitor resistance pathways, and endocrine resistance, which lead to RNA upregulation, HCC promotion, or increased oxidative stress [39]. The AR-independent mechanism includes N6-adenosine-methyltransferase (METTL3) knockdown driven by the upregulation of nuclear receptor liver receptor homolog-1 (LRH-1, NR5A2). This causes resistance to AR antagonists and alters N6-methyladenosine (m6A) as the treatment resistance mechanism, particularly in metastatic prostate cancer [40].

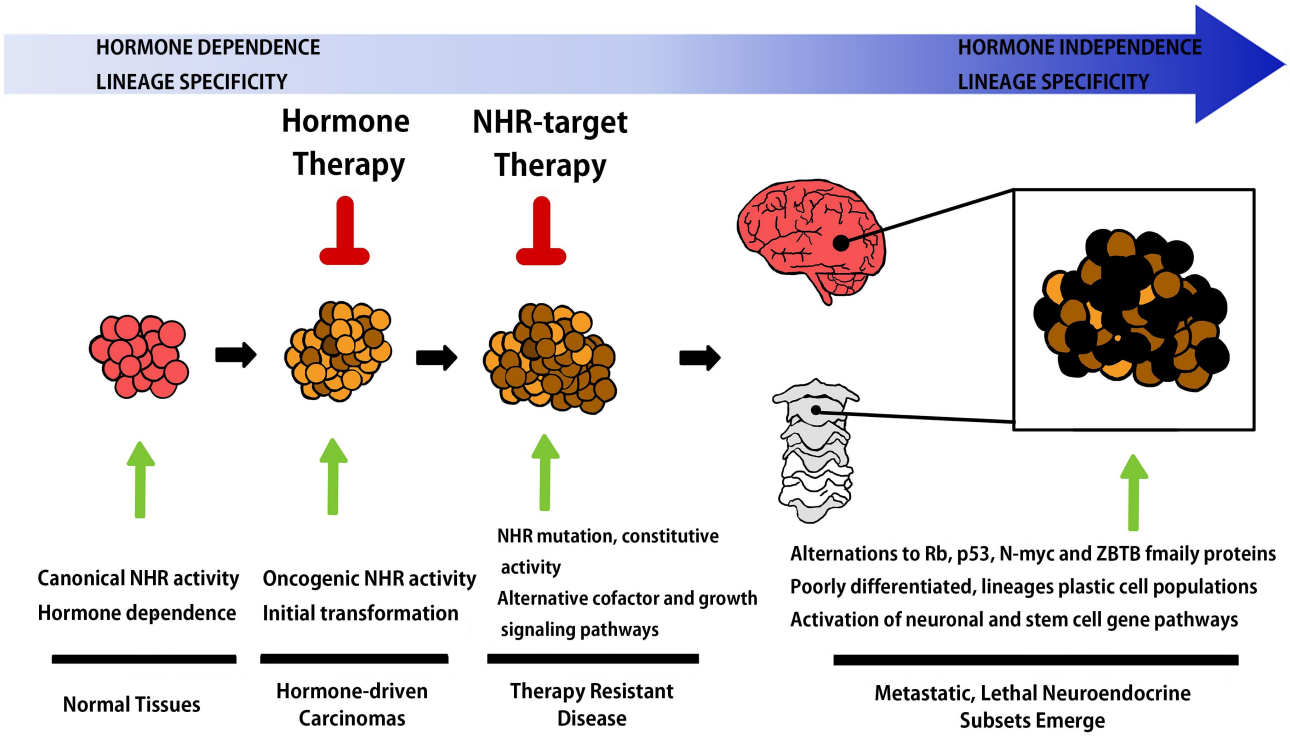

FIGURE 1. Neuroendocrine in hormonal cancer. GnRH, gonadotropin-releasing hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone; NHR, nuclear hormone receptor; ZBTB, zinc finger and BTB domain containing protein.

4. Male gastrointestinal stromal tumor (GIST)

GISTs show variety of molecular alterations and activate KIT and PDGFRA mutations. KIT or PDGFRA-mutated GIST patients depict improved survival with imatinib as the tyrosine kinase inhibitors (TKIs) have higher recurrence risk and are sensitive to imatinib. Other rare subtypes including NF1, SDH gene, B-Raf proto-oncogene, serine/threonine kinase (BRAF) and neurotrophic receptor tyrosine kinase (NTRK) show primary resistance to TKIs which pose challenges for prognosis, prevention, and treatment [41]. KIT mutations have been recognized in 1998 and account for ~70–80% of GISTs. PDGRA mutation is discovered in 2003 and accounts for ~5–10% of GISTs. KIT and PDGRA are mutually beta and activate intracellular signaling pathways via the ligand-independent activation and regulation of cell differentiation, survival, and proliferation. GISTs lacking KIT and PDGRA are referred to as KIT/PDGFRA wild-type GISTs. They are divided into SDH-deficient and non-SDH groups. SDH-deficient group includes Carney triad and Carney-stratakis syndrome, while non-SDH has neurofibromatosis type 1 (NF1) GISTs with BRAF, kirsten rat sarcoma viral oncogene homolog (KRAS), phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) mutations or gene fusions [42]. Carney-stratakis syndrome or dyad is diagnosed at the age of 19–21 years and prevalent in young women with pulmonary, chondrodysplasia, GIST and paraganglioma. Carney triad syndrome is a GIST in children, adolescents, and young adults. Carney-stratakis syndrome and Carney triad bring SDH deficiency, while SDH is preserved in NF1 which is a familial GIST syndrome. SDH deficiency develops resistance to GIST therapeutic TKIs. Above 70% GISTs associated with NF1 syndrome are localized in small intestine contrary to the sporadic GISTs [43].

GIST diagnosis is often late wherein half of the cases fall in malignant and high-risk categories, and require TKI treatment. Abdominal pain and swelling are the frequent symptoms whereas computed tomography (CT) scan and GI endoscopy are the common diagnostic procedures [44]. GIST tumors are in fusiform of ~5 cm size, and characterized by ambiguous symptoms which may lead to misdiagnosis and require combination of chemotherapy and lifelong follow-up [45]. GISTs occur sporadically in elderly of 60–65 years age, with small number in younger adults and children. They occur mostly in elderly, men, blacks, and Asian and Pacific Islanders. It is more asymptomatic with the smaller tumor size. An abdominal mass presence is the main symptom followed by hypoglycemia, biliary obstruction, jaundice and ileus. Intestinal obstruction is common in large tumors with the symptoms of hematemesis and melanotic stools [46]. A clinical trial investigated the efficacy of imatinib in treating GIST where more than half of 91 patients (53%) were males of 60 years age or older having median tumor size of ~6.5 cm. Imatinib treatment of 5 years had no disease recurrence during the treatment and within 2 years of treatment discontinuation. GIST monitoring is thus important [47].

A clinical trial of GIST involving male patient is shown in Table 1 A 61 years male had GIST history which recurred and re-diagnosed 3 years later. He was treated with imatinib 400 mg daily, increased to 800 mg after 6 months, and changed to sunitinib 50 mg daily after 2 years [48]. In the clinical case of 80 years male, recurrence after primary tumor resection of 30-year GIST led to the GI hemorrhagic shock development, and discovered 11.7 cm tumor in duodenal retroperitoneum. Tumor cells were immunoreactive for KIT and discovered on GIST-1 (DOG1). KIT and imatinib treatment was thus employed. A follow-up study was imperative based on the recurrence risk after 10 years of surgical treatment [49]. In another case, 74 years man was presented with 20-pound weight loss, early satiety, and left-sided abdominal pain. CT imaging diagnosed the GIST wherein tumor was invading the diaphragm to lead for surgical treatment followed by 5 years imatinib therapy with sequelae of metastasis in spleen and subsequent dissemination. It presented a case of underlying tumor with splenic bleeding and abdominal pain [50]. In a Scandinavian group, 400 patients at high GIST recurrence risk were treated with adjuvant imatinib 400 mg/day for 1–3 years where localized GISTs were identified. Imatinib survival outcome was confirmed by KIT and PDGFRA mutation analysis in 341 patients with recurrence-free survival [51]. KIT inhibitors employed to treat GIST (imatinib, sunitinib) were the inactive inhibitors. Evaluation of their potential in broad mutational coverage revealed safe coadministration with sunitinib. It was a safe binder for KIT subtypes at 25–37.5 mg daily dose as studied in 39 patients' clinical trial [52]. A 65 years man undergone cholecystectomy in 2017 was presented with abdominal discomfort, weight loss for 5 months, altered bowel habits, black stools, and urinary symptoms. Blood tests were normal, however, CT scan revealed 8.5 × 8.8 × 10.7 cm mass of intra-abdominal GIST. Tumor was removed by pancreaticoduodenectomy which suggested the involvement of duodenum in GIST. The patient herein was also at high risk for GIST, and required adjuvant chemotherapy with tyrosine and imatinib, TKI therapy and repeated CT scans every 3–6 months [53].

5. Future directions

In recent years, therapeutic agents have enhanced the immune response toward anticancer drugs. Gut microbiota is used as an intervention in carcinogenesis mechanism. They have improved the antitumor immunity and therapeutic efficacy. The anti-PD-1 efficacy in reducing T-lymphocytes and antigen 4 (CTLA-4), bifidobacteria and anti-PD-1 in metastatic melanoma patients have been studied. However, there are patients who do not respond [54, 55]. Future therapeutics for GI human cancer thus include the usage of targeted microbiome interventions or nutraceuticals including the natural foods and biotics for diagnosis and treatment of microbiome. Natural foods and biotics prevent cancer and treat specific patients in the clinic through manipulation of microorganisms [56]. Therapeutic approaches include the efficacy enhancement of anti-cancer treatments and modulating the microbiome of proliferation, differentiation, and apoptosis by regulating the mechanisms associated with cells, having role in cancer such as ncRNAs. Nonetheless, dietetics is the most immediate approach. Consumption of fibrous and bioactive foods

TABLE 1. Summary of pivotal clinical case studies on GIST.

Study	Subject	Symptoms	Treatment	Additional findings
Jeong ISD *et al.* [48]	61-year male patient Recurrence after 3 years of GIST resection surgery	Stomach pain	Imatinib 400 mg (first-line treatment), increased to 800 mg after 6 months, sunitinib 50 mg orally maintained	Beware of hyperammonemic encephalopathy in GIST patients without chronic disease. Patients with predisposing comorbidities need awareness of the potential for worsening encephalopathy.
Kanda T *et al.* [49]	80-year male patient Recurrence after 30 years of GIST resection surgery	GI hemorrhagic shock	TKI and imatinib, surgical treatment, 10 years follow-up	A history of mesenchymal tumor diagnosis or low-risk GIST associated with higher recurrence. GIST requires longer follow-up than other malignancies. GIST may recur after more than 10 years of curative surgery.
Calise AC *et al.* [50]	74-year male patient Initial Diagnosis of GIST	20-pound weight loss, early satiety, left abdominal pain	5 years of surgical treatment and imatinib	The common metastatic sites are liver and peritoneum. Diagnostic criterion for GIST is the expression of c-Kit (CD117) antigen or positive CD34 staining.
Joensuu H *et al.* [51]	60–65 years age, 51% of 400 people are male	Not revealed	1 or 3 years of surgical treatment and imatinib	3 years of adjuvant imatinib reduces mortality risk by 66% and increases OS rate by 10 years. Except for mutations (KIT exon 9), adjuvant imatinib is the standard GIST care for high recurrence after surgery.
Wagner *et al.* [52]	39 GIST male patients with mean age of 57 years	Not revealed	PLX9486 (KIT subtype) as 250, 350, 500 or 1000 mg dose in combination with 25 or 37.5 mg sunitinib (2e) in consecutive 28 days cycles	Sunitinib can be safely co-administered as the recommended doses in refractory GIST patients. Co-targeting of the two complementary conformational states of same kinase can safely be accomplished.
Yeap JH *et al.* [53]	65-year male patient High risk for GIST Cholecystectomy in 2017	Abdominal discomfort, weight loss for 5 months, abnormal bowel habits, black stools, urinary symptoms	Pancreaticoduodenectomy and tumor resection, adjuvant chemotherapy with tyrosine (imatinib, KIT), 3–6 repeated CT scans	GIST and the duodenum are related. Anemia can be caused and duodenum may be asymptomatic until the tumor reaches significant size. Chemotherapy acts as an adjuvant to reduce tumor size for facilitating surgery.

GI, gastrointestinal; GIST, gastrointestinal stromal tumor; TKI, tyrosine kinase inhibitor; OS, overall survival; KIT, tyrosine kinase; CT, computed tomography.

protects against GI cancers by modulating MedDietis via the direct intake of pro- and pre-biotic foods [57]. Androgen receptor (AR) as a nuclear transcription factor has role in male sexual differentiation, prostate growth, benign prostatic hyperplasia, prostatitis, and prostate cancer. Natural AR inhibitors are identified in edible plants like fruits, vegetables, folk medicines, health foods, and nutritional supplements [58]. GI cancer is based on abnormal lipid metabolism pertaining to the GI epithelial cell-derived malignancies including gastric and colorectal cancer. Studies suggest that growth, proliferation, and GI cancer cells metastasis can be affected by lipid metabolism reprogramming [59]. Such targeted therapies are based on genetic contributions, and the long non-coding RNAs (lncRNAs) in regulating cell proliferation, cell division, migration, invasiveness, epithelial to mesenchymal transition, and drug resistance in several GI cancers. Maternally expressed gene 3 (MEG3) in GI malignancies is thus of interest and serves as rationale for anticancer therapy [60]. Furthermore, growth-hormone-releasing hormone (GHRH) and GHRH receptor (GHRH-R) can be expressed in tumor tissues, and cell lines, and used as antagonists in treating GI cancers including breast, pancreatic, colon, gastric, prostate, ovarian, and lung [61]. The microbiome is being studied using these novel receptors and cell lines which may ease their utility as biomarkers in future.

6. Conclusions

GI cancer is the malignancy of digestive and GI tract pathways including esophagus, stomach, liver, pancreas, and colon. It is the most prevalent in men. Even though many men experience tumor resection, GI cancer has 5-year prognosis and 10-year recurrence risk that requires monitoring, follow-up, ongoing treatment, and preventive care. Treatment and the management are carried out by imatinib and KIT, however research on targeted treatment of phosphoinositide 3-kinase/protein kinase B/mechanistic target of rapamycin (PI3K/AKT/mTOR) by natural foods and biotics is being prioritized. The development of new therapeutic agents by modifying cell lines, receptors, and genes is being focused. Research in this field continues to progress. Research and clinical trials are being conducted on preventive and treatment management of GI cancer. However, specific clinical case studies on GIST are lacking. This review encompasses a small number of clinical cases. It is imperative to conduct and critically review wide range of studies. Moreover, clinical trials and randomized controlled studies must be conducted on new targeted therapies based on mutated genome, natural product-based therapies, and chemotherapeutic improvements.

ABBREVIATIONS

GI, gastrointestinal; GIST, gastrointestinal stromal tumor; KIT, tyrosine kinase; PDGFRA, platelet-derived growth factor receptor alpha; rHCG, recombinant HCG; AR, androgen receptor; CRC, colorectal cancer; E1, 17β-hydroxysteroids oestrone; E2, oestradiol; EC, esophageal cancer; ALB, albemaie; GC, gastric cancer; MMR, muscle mass ratio; MIDG, minimally invasive distal gastrectomy; HBV, hepatitis B virus; HCV, hepatitis C virus; NAFLD, non-alcoholic fatty liver disease; T2D, type 2 diabetes; PLCs, primary liver cancers; HCC, hepatocellular carcinoma; CC, cholangiocarcinoma; CLD, chronic liver disease; LS, Lynch syndrome; NHR, nuclear hormone receptor; ER, estrogen receptor; pARSER81, phosphorylation at serine 81; ADT, androgen deprivation therapy; DHT, dihydrotestosterone; NRG1, neuregulin1; ENS, enteric nervous system; FGIDs, functional gastrointestinal disorders; DGBI, disorders of gut-brain interaction; CAG, chronic atrophic gastritis; EGFR, estimated glomerular filtration rate; HCC, hepatocellular carcinoma; METTL3, N6-adenosine-methyltransferase; LRH-1, NR5A2, nuclear receptor liver receptor homolog-1; TKIs, tyrosine kinase inhibitors; NF1, neurofibromatosis type 1; SDH, succinate dehydrogenase; CTLA-4, T-lymphocytes and antigen 4; GHRH, growth-hormone-releasing hormone; GHRH-R, growth-hormone-releasing hormone receptor; WT, wild type; CD, Cluster of Differentiation; HCG, Human Chorionic Gonadotropin; ATM, ataxia telangiectasia mutated gene; BRCA, breast cancer; DNA MMR genes, DNA mismatch repair genes; MLH1, mutL homolog 1; MSH2, mutS homolog 2; PMS2, PMS1 homolog 2; XIST, X-inactive specific transcript; BRAF, B-Raf proto-oncogene; NTRK, neurotrophic receptor tyrosine kinase; KRAS, kirsten rat sarcoma viral oncogene homolog; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; CT, computed tomography; PI3K/AKT/mTOR, phosphoinositide 3-kinase/protein kinase B/mechanistic target of rapamycin.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

YP and KHK—Conceptualization, vali-dation, writing-review. YP—methodology, software, formal analysis, investigation, resources, data curation, writing–original draft preparation, editing, visualization. KHK—supervision. All authors have read and agreed to the published version of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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