Gastroesophageal junction and gastroesophageal junction carcinoma : a short update

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Abstract

Cancer of the gastroesophageal junction (GEJ), although rare, is now considered a separate entity with a distinct pathophysiological and molecular profile. Although much progress has been made over the past decades in delineating the multiple environmental and genetic pathways involved GEJ carcinoma, the exact molecular mechanisms underlying disease initiation and progression are still poorly understood. This is of paramount importance for the treating physician as the disease bears a poor therapeutic response. This review defines the GEJ and types of GEJ carcinoma, and provides useful insight in its pathophysiology. Future aspects include better understanding of GEJ oncogenesis, early detection of precursor lesions, the use of biomarkers and targeted therapy (through molecular profiling) so as to increase overall survival. (Acta gastroenterol. belg., **2016**, 79, **471-479**).

Key words : gastroesophageal junction, gastroesophageal junction cancer, pathophysiology, treatment.

Introduction

Cancer of the gastroesophageal junction (GEJ), although rare, is now considered a separate entity with a distinct pathophysiological and molecular profile. This is of paramount importance, since the physician can, even under the spectrum of the same disease, define subgroups of patients who will benefit from particular combined modality approaches (surgery, chemotherapy, radiotherapy) (1). Although much progress has been made over the past decades in delineating the complex pathophysiology behind GEJ carcinoma, the reported clinical studies are not so helpful ; the data reported cannot be interpreted under a uniform manner. The heterogeneous populations studied cannot provide robust data for clinical analysis and interim planning. The site of the tumor (esophageal, GEJ, gastric), the different histological profiles (squamous, adenocarcinoma), as well as differences in staging (computed tomography, endoscopic ultrasound, laparoscopy, positron emission tomography) and treatment protocols are *a priori* binding when trying to exclude solid evidence (2).

This review offers a short update behind GEJ carcinoma ; the incidence, risk factors and prognosis of the disease along with its pathophysiological, molecular and biological background. From a clinical point of view, useful clinical, endoscopic and histological pointers are given so as to aid the treating physician in differentiating GEJ carcinoma from esophageal or gastric cancer, while a brief review of any future treatment aspects is presented. Since the pathophysiological background of GEJ carcinoma is not completely understood, molecular and pathophysiological aspects of satellite lesions (esophageal and gastric adenocarcinoma) that share common pathways in GEJ oncogenesis are, also, presented. However, before elucidating GEJ carcinoma aspects, we believe that we should describe the GEJ itself, as its definition carries significant pitfalls and geographical variations.

Definition of the GEJ

Defining the GEJ is not as simple as the term itself implies, as it has histological, anatomical, and endoscopical components. The borders of the GEJ lie between the distal esophagus and the proximal stomach ; it is the area where the squamous epithelium of the esophagus transitions into the columnar epithelium of the gastric cardia (squamocolumnar junction, SCJ). However this is not always the case, as in patients with gastroesophageal reflux disease (GERD), the lower esophageal sphincter (LES) is shortened and the intraluminal pressure in its intraabdominal portion is lowered, thereby causing dilatation of the distal esophagus (gastricization of the esophagus) and the formation of a hiatal hernia. In Western patients, the SCJ may be displaced proximally from the mucosal EGJ, while it has been shown that in Japanese patients the SCJ overlaps with the mucosal EGJ in most subjects (3,4). The GEJ is the proximal limit of pure oxyntic mucosa ; everything proximal is esophagus. As currently known, the squamous mucosa and deep esophageal glands and ducts are unique to the esophagus and absent in the stomach, rendering these histological landmarks (along with a multilayered epithelium) the gold standard to histologically define the mucosal EGJ (5).

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The most important anatomical landmark when trying to designate the GEJ is the angle of His (the region where the lateral wall of the esophagus meets the medial aspect of the dome of the stomach at an acute angle) (6). Likewise, in patients with severe hiatal hernias or in cases of GEJ carcinomas, the LES is damaged to such an extent that this landmark is also affected (3). Endoscopically, the proximal end of gastric longitudinal mucosal folds and the distal end of the esophageal longitudinal palisading vessels mark the borders of the mucosal GEJ. However, problems in endoscopic identification of the GEJ still arise when dealing with patients with hiatal hernias, when the endoscopist artificially overinflates the gastric mucosal folds or during respiratory movements (for the upper border) or with patients with active esophagitis or in resected or autopsy esophageal specimens (for the lower border) (3,7).

Definition and subtypes of the GEJ carcinoma

According to the World Health Organization (WHO), "*adenocarcinomas that straddle the junction of the oesophagus and stomach are called tumours of the oesophagogastric junction…regardless of where the bulk of the tumour lies. This definition includes many tumours formerly called cancers of the gastric cardia. Squamous cell carcinomas that occur at the oesophagogastric junction are considered carcinomas of the distal oesophagus, even if they cross the oesophagogastric junction junction*" (8).

The classification of the GEJ adenocarcinoma, proposed by Siewert and Stein, 15 years ago is considered valid up to nowadays, as it is useful to base therapeutic decisions. According to it, GEJ adenocarcinoma can be divided into three distinct types in regards to the epicenter (the place of origin) of the tumor (Figure 1). The types proposed along with their characteristics are depicted on Table 1 (9-11). While type I pertains to esophageal cancers (located in the distal esophagus) and type III to gastric cancers (located in the gastric cardia),

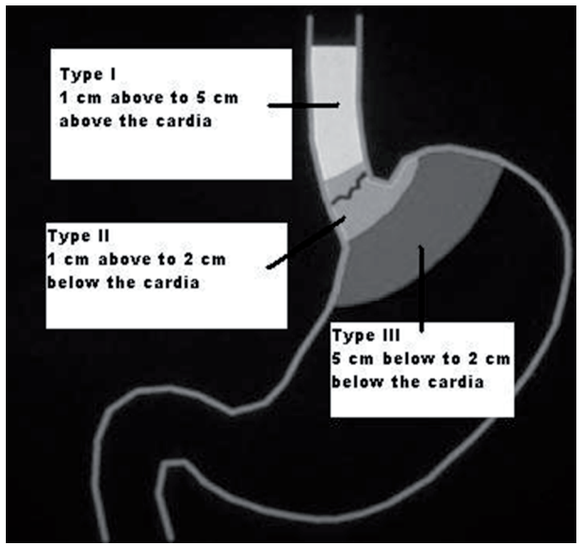

Fig. 1. — GEJ adenocarcinoma types according to the tumor epicenter.

questions regarding type II GEJ cancer etiology, site of origin and behavior (esophageal adenocarcinoma or gastric cancer) have not been answered yet (11).

Due to the similarities described by several authors that gastric cardiac carcinoma and Barrett's esophagus-associated distal esophageal adenocarcinoma share common topographic, epidemiological, pathophysiological and clinical characteristics, as well as common prognosis (12,13), the American Joint Committee on Cancer (AJCC) in its 7th edition staging manual has subsumed tumors of the GEJ into those of the esophagus. *"All other cancers with an epicenter in the stomach greater than 5 cm distal to the EGJ, or those within 5 cm of the EGJ but not extending into the EGJ or esophagus, are stage grouped using the gastric (non-EGJ) cancer staging system"* (14).

Table 1. — **Types of GEJ cancers.**

Type	Epicentre	Patients' characteristics	Histology	Tumor characteristics	Therapy (for locally advanced tumors)
I (adenocarcinoma of the distal esophagus)	1 cm above to 5 cm above the cardia (esophagus)	Male, obese, younger age, association with GERD/Barrett's esophagus	Intestinal type Lauren histology	Similar to esophageal adenocarcinoma; lymphatic vessel invasionnot common	Perioperative or NARCTfollowed by esophagectomy
II (tumors of the cardia or GEJ)	1 cm above to 2 cm below the cardia	Epidemiologicaland histological characteristics intermediate between those of type I andtype III cancers			Esopha-gectomyor extended transhiatal gastrectomy
III (subcardial gastriccarcinoma)	5 cm below to 2 cm below the cardia (stomach)	Less marked male predominance, associated with H. pylori-induced atrophic gastritis and intestinal metaplasia	Intestinal, diffuse or mixed type Lauren histology	Similar with non-cardia gastric cancer ; metastasis to abdominallymph nodes	Perioperative or NECT followed by gastrectomy

GEJ : gastroesophageal junction ; GERD : gastroesophageal reflux disease ; NARCT : neoadjuvant radiochemotherapy ; NECT : neoadjuvant chemotherapy.

Table 2. — **Risk and protective factors for the development of GEJ cancer.**

	OR	**95% CI**
Risk factor		
Smoking	2.18	1.84 - 2.58
Alcohol (?)	0.77 (for ≥ 7 drinks/day)	0.54 - 1.10
GERD	13.0	1.77 - 99
Obesity	3.07 (for BMI ≥ 40)	1.89 - 4.99
Diet	1.8 (for diets high in processed meat, red meat, sweets, and high-fat dairy)	1.1 - 2.9
Protective factor		
H. pylori	0.31	0.11 - 0.89
NSAIDs	0.57	0.39 - 0.83

GEJ : gastroesophageal junction ; OR : odds ratio ; CI : confidence interval ; GERD : gastroesophageal reflux disease ; BMI : body mass index ; *H. pylori : helicobacter pylori* ; NSAIDs : nonsteroidal anti-inflammatory drugs.

Incidence, risk factors, prognosis

There are no robust data regarding the incidence of GEJ carcinomas. The estimated number of new cases regarding esophageal carcinoma in the United States of America (USA) for 2015 is 16,980 (13,570 male : 3,410 female), with 15,590 related deaths (12,600 male : 2,990 female). Out of those, only a small proportion refers to GEJ carcinoma ; the overall incidence of adenocarcinoma of the GEJ is approximately 3.1 per 100,000 (15). Worldwide, squamous cell carcinoma of the esophagus is most common. However, in the USA (along with many Western countries), adenocarcinoma numbers are far higher than squamous cell carcinoma (16). The Surveillance, Epidemiology, and End Results (SEER) cancer registry program in the USA report (1973 to 2008) reveals an approximate 2.5-fold increase in the incidence of GEJ adenocarcinoma from 1973 to 1992 ; these rates appear to be stable over the last 20 years (17).

This rise is attributed mostly to the rise in the incidence of Barrett's esophagus (in patients with GERD), which constitutes the major risk factor for the development of GEJ adenocarcinoma (18). Other risk factors include smoking (despite declining smoking rates in the USA over the last decades), alcohol consumption (despite inconsistent results reported by studies investigating an association between alcohol consumption and GEJ adenocarcinoma), and obesity (although the increase in obesity incidence in Western countries does not seem to correlate with the stable incidence of GEJ adenocarcinomas over the last twenty years). Other risk factors (with weak or modest association with GEJ adenocarcinoma) include the decline in *Helicobacter pylori* (*H. pylori*) prevalence in Western countries (which seems to convey a protective effect against GEJ adenocarcinoma) along with the increasing use of nonsteroidal anti-inflammatory drugs (NSAIDs) which block the inflammatory cascade (crucial in the development of GEJ carcinoma) (19,20). Risk and protective factors for GEJ adenocarcinoma and their respective Odds Ratios (ORs) are summarized on Table 2 (21-27).

Regarding prognosis, the SEER has shown modest improvements in overall 5-year survival ; from 1973 to 1984, the 5-year survival was 8%, from 1985 to 1986, 12%, and from 1997 to 2008, 17% (regarding GEJ adenocarcinoma of any stage) [20]. For early stage locoregional, confined disease, the 5-year survival rate is 25% - 30% (28).

Pathophysiology

Although the Siewert and Stein classification of GEJ tumors is considered by most experts useful as it can be used as an aid to surgical decision-making, its main disadvantage lies on not being able to represent the pathophysiological etiology behind the disease (1,11). Currently, researchers advocate the idea of 2 distinct different pathways responsible for the development of GEJ adenocarcinomas (Figure 2) :

1. the intestinal pathway (where goblet cells becomes dysplastic, i.e. in Barrett's esophagus) and
2. the non-intestinal pathway (where cardiac-type glandular mucosa becomes dysplastic) (29,30).

The aforementioned suggestion lies in the fact that some older clinical studies have reported that intestinal type mucosa-associated GEJ adenocarcinomas (as seen in patients with GERD and Barrett's esophagus) have a better prognosis when compared to patients with cardiac-type mucosa-associated adenocarcinomas (31,32). Newer clinical, epidemiological and histological studies seem to confirm that adenocarcinomas of the GEJ are of two distinct etiologies (esophageal or gastric) (33-35). When comparing esophageal adenocarcinoma with the intestinal subtype of non-cardia gastric adenocarcinoma, the gastric mucosa well clear of the lesion in the latter patients is characterized by pangastritis, atrophy, intestinal metaplasia and low/absent acid secretion. On the contrary, in patients with esophageal adeno-carcinoma, the gastric mucosa is usually healthy (34).

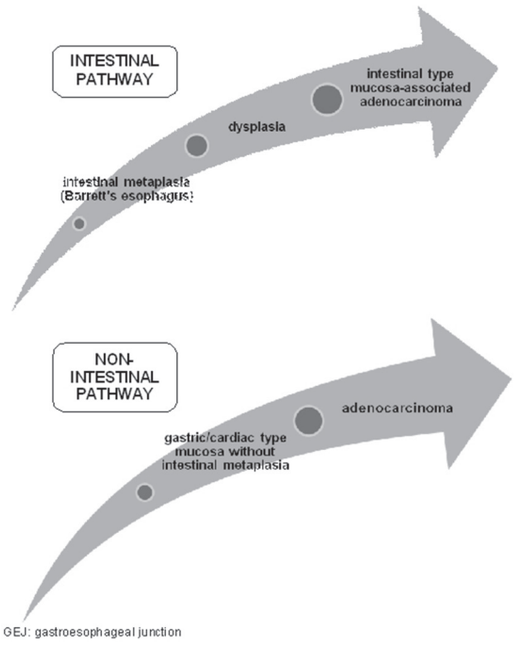

Fig. 2. — The two pathways involved in GEJ carcinoma. GEJ: Gastroesphageal junction

GEJ adenocarcinomas are positively associated with reflux symptoms and gastric atrophy ; however, the association with GERD is confined to those patients without evidence of gastric atrophy (35). From the above, researchers have extrapolated GEJ cancer to be either an esophageal adenocarcinoma probably arising from a Barrett's esophagus or a gastric adenocarcinoma caused by *H. pylori* infection and atrophic gastritis.

However, not all agree with this twofold pathway theory. Some suggest that a cancer arising in the background of gastric/cardiac-type mucosa is nothing more than a large in size tumor that tends to overgrow preexisting short-segment Barrett's esophagus (36). Perhaps, the differences reported in the literature regarding prognosis between these 2 pathways are merely the result of the more effective surveillance protocols carried out by endoscopists (37).

Molecular and biological chara8teristics

Only recently, the Cancer Genome Atlas Research Network proposed 4 subtypes of gastric cancer in an attempt to guide targeted therapies, using an approach readily applied in clinical care. Tumors were either characterized as i) Epstein–Barr virus (EBV)-infected tumors, ii) tumors with microsatellite instability (MSI), iii) genomically stable tumors, and iv) tumors with chromosomal instability (CSI). Each tumor subtype exhibited different molecular characteristics ; (EBV)-infected tumors displayed recurrent *PIK3CA* mutations, extreme DNA hypermethylation, and *JAK2*, *PD-L1* and *PD-L2* amplification. MSI tumors revealed increased mutation rates of genes encoding oncogenic signalling proteins and hypermethylation (including hypermethylation at the *MLH1* promoter). Genomically stable tumors, exhibited recurrent *RHOA* and *CLDN18* events. Last but not least, CIN tumors (which accounted for half of all gastric cancers) showed marked aneuploidy, expression of *p53* (consistent with frequent *TP53* mutation) and focal amplification of receptor tyrosine kinases (RTKs). This classification of distinct salient genomic features (serving as a valuable adjunct to histopathology), could stratify distinct populations of gastric cancer patients in clinical trials that could benefit from targeted therapies (38).

Regarding esophageal adenocarcinoma, functional analyses of esophageal adenocarcinoma-derived mutations in *ELMO1* (a dimerization and intracellular mediator of the Rho family GTPase, *RAC1*) revealed increased cellular invasion, suggesting a new hypothesis about the potential activation of the *RAC1* pathway as a contributor to esophageal adenocarcinoma tumorigenesis (39).

GEJ adenocarcinoma is characterized by significant differences regarding molecular and biological phenotype depending on whether the intestinal pathway is involved or not. Intestinal-type mucosa associated adenocarcinomas are more likely to express nuclear b-catenin while non-intestinal mucosa-associated adenocarcinomas are more likely to correlate with epidermal growth factor receptor (EGFR) amplification (30). Intestinal-type mucosa-associated adenocarcinoma is, also, associated with CDX2 expression ; on the other hand, Barrett's esophagus-related dysplasia has been associated with a decrease in CDX2 expression (40).

From Barrett's to adenocarcinoma

Barrett's esophagus is thought to progress to esophageal adenocarcinoma through a step-wise progression with loss of *CDKN2A* followed by *p53* inactivation and aneuploidy. However, Stachler *et al*, went one step further revealing that oncogene amplification occurs as a late event and that *TP53* mutations often occur early in Barrett's progression, thereby postulating the theory that esophageal adenocarcinoma can emerge not through gradual accumulation of tumor suppressor alterations but rather through a more direct path whereby a *TP53*-mutant cell undergoes genome doubling, followed by acquisition of oncogenic amplifications (41).

What is the molecular mechanism behind the transformation of a squamous epithelial cell to a Barrett's metaplastic cell? Although not exactly defined, many aspects of this complex pathway have been elucidated (Figure 3) (42). As already stated above, most researchers advocate the concept of esophageal stem cells diversion to produce an intestine-like epithelium (transcommitment hypothesis). Normally, esophageal stem cells produce

(by division) 2 different types of cells : a stem cell and a transit cell that will eventually divide on its own so as to differentiate into other cell types. However, in GERD patients, a stem cell of a Barrett's esophagus divides to produce two further metaplastic stem cells. This can happen i) either through gland bifurcation or ii) through lateral migration of glandular tissue which colonizes tissue areas by proliferation (42-44).

However, major downsides to this hypothesis are not only the fact that the potential of stem cells conversion into epithelial tissues populations has not been experimentally proved but, also, that not all stem cell in Barrett's glands give rise to metaplastic epithelium. Therefore, a novel mechanism of oncogenesis postulates the colonization of GEJ regions that become denuded by GERD by residual embryonic cells (RECs) ; the end result is intestinal metaplasia within days of esophageal injury (45). Other theories postulate the colonization of mucosal breaks in the esophagus by stem cells that re-differentiate into metaplastic cells (46). Major genetic and epigenetic changes involved in the carcinogenesis pathway are highlighted in Table 3 and Figure 4 (41,47-52).

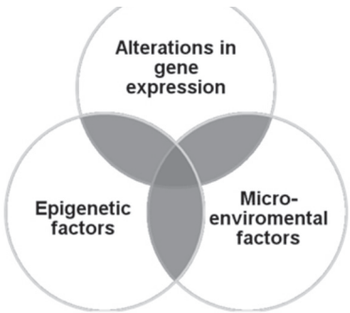

Fig. 3. — Factors implicated in the transformation of a squamous epithelial cell to a Barrett's metaplastic cell. Alterations in gene expression include p53, p16, and cyclin D1 mutations, aneuploidy, APC loss of heterozygosity. Epigenetic factors include increases expression of Cdx1 and Cdx2. Microenviromental factors include bile acids, pH changes, gastrin, inflammatory response.

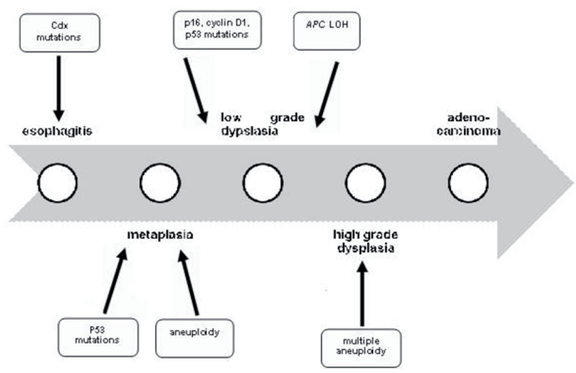

Fig. 4. — The timing of genetic changes in the sequence of malignant transformation. LOH: loss of heterozygosity

Researchers have well established the role of inflammatory microenviromental mediators as the driving force in the carcinogenic pathway of the Barrett's esophagus, described above. On one side, nitric oxide (NO), implicated in DNA damage induction and aberrant cell signaling in various precancerous lesions and on the other, bile acids, a well known inflammatory mediator that, also, induces DNA damage have been identified as mediators in the development of esophageal adenocarcinoma secondary to Barrett's esophagus and reflux disease. Bile acids present in the refluxate induce nitric oxide synthase (NOS) gene and protein expression, thereby generating NO in esophageal cells (53,54).

How to differentiate GEJ carcinoma from esophageal or gastric cancer

Having in mind that is practically impossible for the treating physician to label a lesion in the proximity of the GEJ as GEJ, esophageal or gastric cancer simply from an endoscopic and pathological point of view, attempts have been made, through immunohistochemistry (cytokeratins 7/20 - CK 7/20, and mucin peptide core antigens 1/2/5AC - MPCA 1/2/5AC) and comparative genomic hybridizations (deletion of 14q31-32.1), to provide data that would help determining the origin of the adenocarcinomas of the intestinal histological subtype. For example, Shearer *et al*, report that type I adenocarcinoma expresses Barrett's CK7/20 pattern, type II a gastric CK7/20 pattern, and type III a mixture of Barrett's and gastric CK7/20 pattern with intestinal metaplasia (55). However, results are inconsistent and cannot be used in clinical practice (11,56,57).

McColl and Going suggest that when it comes to delineating whether an intestinal type GEJ adenocarcinoma is of esophageal or gastric origin, the treating physician should rely on a thorough recording of the patient's history as well on the histology report of the stomach wall clear of the cancerous lesion. Regarding the former, a positive GERD history should point to an esophageal adenocarcinoma. As far as the latter is concerned, the endoscopist should take biopsy samples (apart of the lesion itself) from the gastric antrum and corpus ; signs of atrophy, intestinal metaplasia and body-predominant gastritis, strongly suggest a gastric origin adenocarcinoma (11).

Future aspects

Chemotherapy (besides surgery for locally advanced tumors) remains the cornerstone of treatment. However,

Table 3. — **Major genetic and epigenetic changes involved in the carcinogenesis pathway.**

Changes	Role	Action	Comment
p53 mutations	Tumor suppressor gene - regulates cellular proliferation and apoptosis	Blocks cells in the G0 and G1phases of the cell cycle, and apoptosis by impinging on the Bax and PIG3 reporterpathways	p53 accumulation due to aneuploidy/ abnormalities in chromosomal content
Cdx1, Cdx2 loss of function	Members of the caudal-related homeobox transcription factor gene family	Regulation of tissue differentiation and development(intestinal homeostasis).Replacement of intestinal cells with a stratified squamous phenotype	Enhanced expression of Cdx1, Cdx2following exposure to bile acids, TNF-a, IL-1b
Sox2 loss of function	Member of the *Sry*-like high mobility group domain protein family - transcription factor	plays a role in the formation of goblet cells	It's down-regulation is associated with intestinal metaplasia in the stomach
Overexpression of cyclins D and E	Members of the cyclin protein family -regulate cellular proliferation	Loss of cell cycle progression promotion	Cyclin D1 normally complexes withCDK4 and cyclin E with CDK2 to phosphorylatethe Rb protein
Mutation, LOH or promoter hypermethylation of p16	Tumor suppressor gene - regulates cellular proliferation	Decelerates cell progression from G1 to S phase	p16 hypermethylationcorrelates with the degree of dysplasia in specialised intestinal metaplasia
Amplification of EGF-R and TGF-a	Growth factors - stimulate an increase in cell proliferation	Located on chromosomes7p12-13 and 2p13, respectively, which are frequently amplified in esophageal adenocarcinomascorrelating with lymphatic dissemination	Correlation to poorly differentiated esophagealadenocarcinomas and to a decrease in survival rate
Overexpression of HGF-R	growth factor receptor - role in embryonic organ development, organ regeneration and wound healing	Activates a tyrosine kinase signaling cascade after binding to the proto-oncogenic c-Met receptor	HGF-R negativeesophageal tumors have a increased survival rate

TNF-a : tumour necrosis factor-a ; IL-1b : interleukin-1b ; CDK : cyclin dependent kinase ; Rb : retinoblastoma ; EGF : epidermal growth factor ; TGF-a : transforming growth factor-a ; PIG3 : phosphatidylinositol glycan 3 ; LOH : loss of heterozygosity ; HGF-R : hepatocyte growth factor receptor.

treatment with a combination of cytotoxic agents (platinum, taxanes, anthracyclines, etc) has yielded only mild improvements in patient overall survival (58). Given the fact that GEJ carcinoma is highly aggressive, more and more molecular profiling studies have been undertaken so as to delineate the molecular signature of the tumor. Gene expression and DNA sequencing studies have helped to categorize patients with GEJ cancer into different subtypes which seem to respond better to targeted therapies. Numerous preclinical studies with a variety of agents targeting the various signaling pathways involved in GEJ oncogenesis like growth factor receptors, mediators of intracellular signal transduction, angiogenic pathways and adhesion molecules have yielded promising results (Table 4) ; the next logical thing is to implement the aforementioned targeted regimens in clinical trials (58-61).

HER2, a member of the EGFR family, responsible for transmitting signals from the cell surface to the nucleus, plays a crucial role in cellular proliferation, differentiation, growth, survival, apoptosis and angiogenesis. However, a variety of mutations regarding the expression of HER2 can deregulate one or more of these biological processes, leading to oncogenesis and metastasis (62). Numerous studies have revealed HER2 overexpression in 2%-45% of gastric cancer and GEJ adenocarcinoma patients (63,64). Trastuzumab is a monoclonal antibody which specifically targets HER2 protein by directly binding the extracellular domain of the receptor. The combination of trastuzumab and a platinum/fluropyrimidine based chemotherapy has demonstrated a survival advantage, rendering the aforementioned scheme the *sine qua non* in patients with for HER2 positive advanced gastric or GEJ cancer (median OS of 13.8 months when trastuzumab was added to capecitabine plus cisplatin or fluorouracil versus 11.1 months when trastuzumab was omitted from the chemotherapeutic regimen) (65,66).

Immunotherapy is a novel and promising alternative for targeting cell programmed death with encouraging preclinical data. As tumor cells use regulatory checkpoints as a means to activate the immune system in order to escape immunosurveillance, interaction between program death-1 (PD-1) and program death-ligand 1 (PD-L1) can lead the activated T cell to a state of anergy. Multiple anti-PD-1 (nivolumab, pembrolizumab) and anti-PD-L1 monoclonal antibodies (MPDL3280A, Medi4736) are under evaluation in digestive cancers (67).

To date, no biomarker used in everyday practice in patients with GEJ carcinoma has been shown to carry prognostic or predictive value in the perioperative setting (65). However, in the near future, HER2 and MET tyrosine kinase could have prognostic value as many studies have reported that HER2 amplification and

Table 4. — **Characteristic examples of targeted therapies in preclinical studies.**

Class	Agent
VEGFR inhibitors – TKIs – Monoclonal antibodies	– Sunitinib, sorafenib, pazopanib – Bevacizumab
HER2 inhibitors – TKIs – Monoclonal antibodies	– Trastuzumab – Lapatinib
EGFR inhibitors – TKIs – Monoclonal antibodies	– Erlotinib, gefitinib – Cetuximab, panitumumab
c-MET inhibitors – TKIs – Monoclonal antibodies	– Foretinib – Rilotumumab
PARP inhibitors	– Olaparib
IGF-1 inhibitors	– CP-751,871
FGF TKIs	– AZD2171
PI3 kinase inhibitors	– Everolimus
GCC inhibitors	– MLN0264
Immunotherapy – anti-PD-1 – anti-PD-L1 monoclonal antibodies	– Nivolumab, pembrolizumab – MPDL3280A, Medi4736

TKI : tyrosine kinase inhibitor ; VEGFR : vascular endothelial growth factor receptor ; EGFR : epidermal growth factor receptor ; HER2 : human epidermal growth factor receptor 2 ; PARP : poly-adenosine diphosphate ribose polymerase ; FFG : fibroblast growth factor ; PI3 : phosphoinositide 3 ; GCC : guanylyl cyclase C ; PD-1 : program death-1 ; PD-L1 : program death-ligand 1.

MET copy number gain carry an unfavorable prognosis (69-71).

Conclusions and prospects for future research

GEJ cancer is influenced by gene-environment interactions resulting in activation of multiple molecular pathways. Unfortunately, up to date, these molecular mechanisms underlying disease initiation are still poorly understood. GEJ adenocarcinoma is highly aggressive ; if surgically resectable the prognosis is good. However, when unresectable, most treatment regimens offer small or even no survival benefit. The complex pathophysiological cascade mentioned above is thought to be responsible for the poor treatment response. Therefore, it seems that early detection, identification of possible precursor lesions and dissertation of premalignant from malignant lesions remains the only means of preventing deaths (72).

High density genomic profiling arrays using next generation sequencing (NGS) can identify patients that could benefit from a targeted therapy. New clinical studies should not attempt to use a "one size fits all" approach ; on the contrary, trial enrollment should include subtypes of patients (with a specific molecular profile) that would, probably, benefit the most from targeted therapies. Personalized care should include the use of predictive and prognostic biomarkers that could predict the efficacy of cytotoxic agents and avoid primary and acquired resistance.

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