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Adénocarcinome à cellules peu cohésives: revue exhaustive de la littérature.

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AVERTISSEMENT

La Faculté n’entend donner aucune approbation aux opinions émises dans les thèses: celles-ci sont propres à leurs auteurs.

Le train de ma vie.

A la naissance, on monte dans le train et on rencontre nos Parents.
On croit qu'ils voyageront toujours avec nous.
Pourtant, à une station, nos Parents descendront du train,
nous laissant seuls continuer le voyage.
Au fur et à mesure que le temps passe, d'autres personnes montent dans le train.
Et elles seront importantes :
notre fratrie, nos amis, nos enfants, même l'amour de notre vie.
Beaucoup démissionneront (même éventuellement l'amour de notre vie), et laisseront un vide plus ou moins grand.
D'autres seront si discrets qu'on ne réalisera pas qu'ils ont quitté leurs sièges.
Ce voyage en train sera plein de joies, de peines, d'attentes, de bonjours, d'au-revoir et d'adieux.
Le succès est d'avoir de bonnes relations avec tous les passagers
pourvu qu'on donne le meilleur de nous-mêmes.
On ne sait pas à quelle station nous descendrons,
donc vivons.
Il est important de le faire car lorsque nous descendrons du train,
nous ne devrons laisser que de beaux souvenirs
à ceux qui continueront leur voyage.
Soyons heureux avec ce que nous avons et remercions le ciel
de ce voyage fantastique.
Aussi merci d'être un des passagers de mon train.
Et si je dois descendre à la prochaine station,
je suis content d'avoir fait un bout de chemin avec vous.
Je veux dire à chaque personne qui lira ce texte
que je vous remercie d'être dans ma vie et de voyager dans mon train.

Jean d'Ormesson

Liste des abréviations

ADCI: Adenocarcinome à Cellules Indépendantes
CHIP: Chimio-Hyperthermie-Intra-Péritonéale
ECF: Epirubicine-Cisplatine-5-Fluorouracile infusionnel
FLOT: 5-Fluorouracile, Leucovorine, Oxaliplatine et docéTaxel
OMS: Organisation Mondiale de la Santé
PIPAC: chimiothérapie intrapéritonéale pressurisée par aérosols

List of abbreviations

5-FU: 5-Fluorouracil
95% CI: Confidence Interval of 95%
ACTS-GC: Adjuvant Chemotherapy trial of TS-1 for Gastric Cancer
AGC: Advanced Gastric Cancer
CRT: Chemo-RadioTherapy
CT: ChemoTherapy
CRS: CytoReductive Surgery
DCF: Docextaxel-Cisplatin-5-Fluorouracil
DFS: Disease-Free Survival
DGC: Diffuse Gastric Cancer
EBV: Epstein–Barr vVrus
ECF: Epirubicin-Cisplatin-infusional-5-Fluorouracil
ECX: Epirubicin-Cisplatin-Capecitabine
EGC: Early Gastric Cancer
EGFR: Epidermal Growh Factor Receptor
EMR: Endoscopic Mucosal Resection
EOF: Epirubin-Oxaliplatin-infusional-5-Fluorouracil
EOX: Epirubicin-Oxaliplatin-Capecitabine
ER: Endoscopic Resection
ESD: Endoscopic Submucosal Dissestion
ESMO: European Society for Medical Oncology
FDG: Fluoro-2-Deoxy-D-Glucose
FLOT: 5-fluorouracil, leucovorin, oxaliplatin and docetaxel
GA: Gastric Adenocarcinoma
GC: Gastric Cancer
GEA: Gastro-Esophageal Adenocarcinoma
GEJ: GastroEsophageal Junction
GIRCG: Italian Research Group for Gastric Cancer
HDGC: Hereditary Diffuse Gastric Carcinoma
HER2: Human Epidermal growth factor Receptor 2
HIPEC: Hyperteermic IntraPEritoneal Chemotherapy
HR: Hazard Ratio
IGCLC: International Gastric Cancer Linkage Consortium

JCOG: Japan Clinical Oncology Group study
JGCA: Japanese Gastric Cancer Association
LBC: Lobular Breast Cancer
LNM: Lymph Node Metastasis
LP: Linitis Plastica
LVI: Lympho-Vascular Invasion
MAC: Mucinous AdenoCarcinoma
MSI: MicroSatellite Instability
NCCN: National Comprehensive Cancer Network
OR: Odds Ratio
OS: Overall Survival
PC: Peritoneal Carcinomatosis
PCC: Poorly Cohesive Cells
PCCC: Poorly Cohesive Cells Carcinoma
PCC-NOS: Poorly Cohesive Cells Not Otherwise Specified
PCI: Peritoneal Cancer Index
pCR: pathological Complete Response
PET: Positron Emission Tomography
PD: Poorly Differentiated
PIPAC: Pressurized IntraPeritoneal Aerosol Chemotherapy
PTG: Prophylactic Total Gastrectomy
R0 resection: no cancer cells seen microscopically at the resection margin
RCT: Randomized Controlled Trial
RT: RadioTherapy
SEER: Surveillance, Epidemiology, and End Results
SDGC: Sporadic Diffuse Gastric Cancer
SG: Subtotal Gastrectomy
SGC: Scirrhous Gastric Carcinoma
SRCC: Signet Ring Cells Carcinoma
SRC-CRC: colorectal cancer with signet ring cells
SRC-GC: Gastric Cancer with Signet Ring Cells
SRC-EC: Esophageal Cancer with Signet Ring Cells
SUV: Standard Uptake Value
TCGA: The Cancer Genome Atlas
TG: Total Gastrectomy
TNM: Tumor, Node, Metastasis
UL: ulcerative findings
UND: undifferentiated
VEGF: Vascular Endothelial Growth Factor
WHO: World Health Organization
WMD: Well- and Moderately-Differentiated

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Résumé

Introduction: Alors que l'incidence du cancer de l'estomac décroit depuis les dernières décennies, celle de l'adénocarcinome à cellules indépendantes (ADCI) est en constante augmentation. Ce type histologique individualisé dans la classification OMS semble avoir des caractéristiques distinctes des autres types d'adénocarcinomes gastriques. Le but de cette revue était de réaliser une mise au point sur les données publiées sur l'ADCI gastrique principalement mais aussi sur les autres localisations, notamment colorectale et oesophagienne.

Méthode: Une revue exhaustive de la littérature publiée en langue Anglaise entre 1980 et avril 2018 a été réalisée en utilisant les termes suivants: "signet ring cell carcinoma", "poorly cohesive cells", "Laurén and diffuse type", "linitis plastica" et "Borrmann type IV".

Résultats: La définition histologique de l'ADCI a été évolutive au cours du temps et correspond sur le plan moléculaire essentiellement aux tumeurs génomiquement stables. L'évaluation du contingent tumoral à cellules indépendantes semble d'intérêt sur le plan pronostique. Cette valeur pronostique reste toujours débattue mais paraît dépendante du stade de la maladie : pronostic meilleur ou équivalent en cas de cancer superficiel et pronostic plus péjoratif avec un tropisme ganglionnaire et péritonéal marqué et un risque d'envahissement des marges longitudinales majoré en cas de tumeur plus évoluée. Ces caractéristiques sont également retrouvées dans les localisations tumorales non gastriques. Ces éléments suggèrent la nécessité d'une adaptation du bilan (coelioscopie exploratrice systématique) et du traitement avec (i) des indications de traitement endoscopique restreintes, (ii) une adaptation du geste chirurgical notamment en terme de marges. La place des traitements intra-péritonéaux (CHIP, PIPAC) est en cours d'évaluation. Plusieurs études ont évoqué une chimiorésistance des ADCI. Les résultats de l'essai de phase II PRODIGE 19 évaluant l'intérêt d'un changement de stratégie dans les ADCI sont en attente. Des données préliminaires suggèrent une meilleure efficacité du FLOT par rapport à l'ECF dans les ADCI.

Conclusion: L'ADCI est une entité histologique individualisée dont les caractéristiques sont distinctes des autres types d'adénocarcinomes. L'individualisation des ADCI dans les essais en cours et futurs permettra d'évaluer la nécessité de proposer une stratégie thérapeutique adaptée afin d'essayer d'améliorer la survie des patients.

Introduction générale

Alors que l'incidence mondiale du cancer de l'estomac décroit ces dernières décennies, l'incidence de l'adénocarcinome à cellules indépendantes (ADCI) est en augmentation principalement dans les pays occidentaux (1-12). La localisation gastrique de l'ADCI est la plus fréquente des localisations digestives et représente une proportion de plus d'un tiers des adénocarcinomes gastriques dans de récentes grandes séries chirurgicales occidentales (13-16). Les ADCI d'origine colorectale sont rares (1% des cancers colorectaux) (24, 25) mais représentent la 2^{e} localisation suivie en 3^{e} position par les ADCI de l'œsophage (26). D'autres localisations existent mais restent exceptionnelles et sont reportées de manière isolée (519-525).

L'adénocarcinome gastrique présente une importante hétérogénéité d'un point de vue cellulaire et architectural avec notamment la coexistence fréquente de différents composants histologiques (17). Le type ADCI (ou adénocarcinome à cellules en bague à chaton) a été défini en 1977 par la classification de l'Organisation Mondiale de la Santé (OMS) comme une tumeur dans laquelle existe un contingent majoritaire de cellules peu cohésives (>50%) (18).

Différentes études ont souligné que l'ADCI a des caractéristiques propres notamment en terme d'épidémiologie, de présentation au diagnostic, de progression tumorale mais aussi d'un point de vue pronostic et de réponse aux différentes thérapeutiques. L'ensemble de ces données suggérent que l'ADCI devrait être considéré comme une entité à part entière (14, 15, 22, 23). Deux classifications des types histologiques de cancer de l'estomac sont principalement utilisées dans la littérature : celle de Laurén (20) dans laquelle l'ADCI est corrélé au sous type « diffus » et la classification de l'OMS.

Parmis les autres classifications, l'ADCI se rapproche du groupe « infiltratif » de la classification de Ming (21).

La définition de l'ADCI a cependant évolué à travers les différentes classifications de l'OMS et fait maintenant partie d'une entité que l'on appelle adénocarcinome à cellules peu cohésives (19).

L'ensemble de ces différentes définitions entraine, dans la littérature, une imprécision et une confusion sur le terme ADCI, ce qui rend difficile l'interprétation des résultats.

Le but de cette revue était de réaliser une mise au point sur les données publiées sur l'ADCI gastrique principalement mais aussi dans les autres localisations, notamment colorectale et oesophagienne.

ARTICLE

SIGNET RING CELL DIGESTIVE CARCINOMA: A DISTINCT ENTITY?

Category: Review

Projet de publication

ABSTRACT

INTRODUCTION: While the incidence of gastric cancer has decreased worldwide in recent decades, the incidence of signet ring cell carcinoma (SRCC) is rising. This histologic subtype identified in the WHO classification seems to have distinct characteristics from other gastric adenocarcinoma. The aim of this work was to provide an update focusing on SRCC in a systematic review mainly focusing on gastric location.

METHOD: Published data in English between January 1980, and April 2018 were identified from Medline with the search terms “signet ring cell carcinoma”, “poorly cohesive cells”, “Laurén and diffuse type”, “linitis plastica”, “Borrmann type IV“. Additional articles were found by a manual search for references from the already identified articles.

RESULTS: Definition of gastric SRCC has evolved last decades and corresponds mostly to genomically stable tumor based on the molecular classification. The proportion of the SRC component has shown some interest in the prognosis but is still a matter of debate. This prognostic value seems to depend on the stage of the disease. Early gastric SRCC have either an equivalent or a better prognosis than non-SRCC. In contrast, advanced gastric SRCC show a poorer prognosis with a greater propensity for lymph node involvement, peritoneal spreading and positive resection margins. These characteristics are also found in other locations of SRCC. These findings suggest the need of a specific therapeutic strategy in SRCC with (i) larger indications for staging laparoscopy, (ii) more restricted indications of endoscopic resection, and (iii) an adjustment of surgical resection in order to allow curative surgery. The place of intra-peritoneal therapies (HIPEC, PIPAC) is currently under investigations. Several studies have suggested a chemoresistance of SRCC. The results of the phase II trial PRODIGE 19 assessing the interest of another strategy in gastric SRCC are awaited. Preliminaries data suggest a better efficiency of taxanes-based regimens (FLOT) compared to the classic scheme (ECF) in gastric SRCC.

CONCLUSION: SRCC is a specific entity individualized with distinct characteristics compared to other adenocarcinoma. Subgroup analysis of SRCC in current and future trials will allow a strict evaluation to confirm the need of a modified therapeutic strategy in order to improve patient outcomes.

Introduction

A rising incidence of digestive signet ring cells carcinoma (SRCC), has been recently observed for unknown reasons (1–12). Among different digestive tumor locations, gastric SRCC location is the most frequent and best studied. Gastric SRCC (SRC-GC) incidence has recently dramatically increased mainly in Western countries representing at least one third of gastric adenocarcinomas (GA) in recent large surgical series (13–16).

GA demonstrates marked heterogeneity at both architectural and cytologic levels with frequent coexistence of several histologic components (17). Since the first edition of the World Health Organization (WHO) classification of gastric cancer (GC) in 1977 (18), SRCC constitutes one specific histotype and therefore can be better identified among GC

The definition of SRCC has however evolved across the different editions of the WHO classifications and corresponds now to the poorly cohesive cells carcinomas (PCCC) (19). When looking at previous classifications, SRCC is close to “diffuse ” or “mixed” type of Laurén’s classification (20), “infiltrative type” of Ming’s classification (21). However, not all GA classified as “undifferentiated” or “diffuse” are SRCC. Those multiple definitions make difficult to assess this subtype of GA.

Several clinical reports have underlined that SRC-GC behave as separate entitity regarding tumor spreading, tumor response and prognosis suggesting that this subtype of tumor should be individualized (14,15,22,23). As concerns other digestive tumor locations, reports have been scarced, concerning mostly colorectal (24,25) and esophageal tumors (26) and also suggested that SRCC behave in a different way.

Following the complexity regarding the histological definitions and the potential major clinical impact for the patients treatment there was an urgent need to address SRCC in a specific review. In this report we provide an update focusing on SRC-GC presentation and treatment strategies on the basis of an extensive review of the literature. Other digestive tumor locations will be discussed.

Method

Published data in English between January 1980, and April 2018 were identified from Medline with the search terms “signet ring cell carcinoma” (n=3345), “poorly cohesive cells” (n=136), “Laurén and diffuse type” (n=257), “linitis plastica” (n=423), “Borrmann type IV“ (n=178). We also scanned the reference lists of relevant reports. Results were restricted to journal articles (excluding case reports) published in English between January 1980, and April 2018, in which adults (age ≥19 years) were studied. We placed primary emphasis on reports with at least 30 SRCC and supplemented them with smaller studies when data were limited. Additional articles were found by a manual search for references from the already identified articles. Abstracts and reports from meetings were included only when they gave useful, new information regarding treatment of SRCC. Data abstraction was done by both authors; studies were only included with both authors’ agreement (VD, GP).

Definitions of SRCC and classifications

Several classifications have been described for GA however, WHO and Laurén’s classifications are mainly used.

Laurén’s classification

The oldest and more widespread classification for GA is the Laurén’s classification (20). Lesions are classified into one of two major types (intestinal/diffuse). The intestinal type is characterized by cohesive neoplastic cells organized in well-differentiated glandular structures while the diffuse one consisting of poorly cohesive cells (PCC), that may have signet ring morphology, diffusely infiltrating the gastric wall with little or no gland formation. These cells usually appear round and small, either arranged as single cells or clustered in abortive, lacy gland-like or reticular formations. These tumors resemble those classified, as SRCC in the WHO classification with a low mitotic rate and a more pronounced desmoplasia.

Tumors that contain approximately equal quantities of intestinal and diffuse components are called mixed/unclassified carcinomas and represent approximately 10% to 20% of GA (3,27–33). Intestinal and diffuse histotypes present differences in epidemiologic and pathogenetic features, as well as biological-molecular characteristics (30,34–36).

Intestinal type is more common in men and older people (30) and is often related to environmental factors such as *Helicobacter pylori* infection with consequent chronic inflammation and atrophic gastritis, diet, and life style (37,38). Diffuse type occurs more commonly in women and young patients (30,39,40) and is usually independent from inflammation processes (37). Diffuse type can be hereditary, as a result of germline mutation of the gene coding for E-cadherin protein (41). Limitation of this classification is a low interobserver reliability (42,43) especially regarding the mixed/undefined category.

WHO classifications

The WHO classification is based on morphologic features of the predominant component. The most recent version of the WHO classification (4th edition 2010) recognizes four major histologic patterns of GA: (19)

- tubular which are graded as well-, moderately- and poorly-differentiated (WMD and PD) according to the degree of glandular formation,
- papillary (usually classified as well-differentiated),
- mucinous adenocarcinoma (MAC)
- PCC including SRCC, poorly cohesive cells not otherwise specified (PCC-NOS), plus uncommon histologic variants.

Tubular adenocarcinoma is the most common histologic type of early GC. It tends to form polypoid or fungating masses grossly (37). Papillary adenocarcinoma is another common histologic variant often seen in early GC. It tends to affect older people, occurs in the proximal stomach, and is frequently associated with liver metastasis and a higher rate of lymph node metastasis (37). MAC is characterized histologically by extracellular mucinous pools, which constitute at least 50% of tumor volume. The tumor cells can form glandular architecture and irregular cell clusters, with occasional scattered SRC floating in the mucinous pools. Of note, MAC could be misclassified as SRCC (44) leading to confusing data regarding those two distinct histological subtypes (45).

The WHO definition of SRCC evolved across the different editions of classification. The first edition (1977) (18) defined SRCC as a tumor in which more than 50% of the tumor consists of isolated or small groups of malignant cells containing intracytoplasmic mucin. Four morphological SRC types were defined. The 3rd edition (2000) (46) described five morphological SRC types. In the 4th edition (2010), the category SRCC was dropped entirely and SRCC is now currently classified as a subtype of PCC. SRCC is composed predominantly or exclusively of signet-ring-cells characterized by a central optically clear,

globoid droplet of cytoplasmic mucin with an eccentrically placed nucleus. All other poorly cohesive cells in GA that do not display this specific morphology should be defined as PCC-NOS. In some cases, SRC may be restricted to the mucosa in combination with other variants of PCC within the deeper levels of the gastric wall. Of note, SRCC and other PCC are often composed of a mixture of SRC and non-SRC (37). Whether we should consider tumors with a minor component of SRC more likely being like SRCC or not remains unsolved.

Recent evolution

A multidisciplinary international expert group of clinicians and pathologists invited by the European Chapter of the International Gastric Cancer Association met in March 2017 in Verona (Italy) to discuss the topic and establish a consensus on SRC-GC based on the current knowledge to enable standardised prospective studies in the near future (47).

Regarding the definition the following statements have been made:

SRC-GC are defined according to the last WHO classification (2010) as a PCCC containing predominantly or exclusively SRC.

In order to standardize the definition of SRC tumors, it is proposed that only PCCC with almost exclusive SRC morphology (more than 90% of PCC having the SRC morphology) should be classified as SRCC. Other categories are described in table 1.

To date, the prognostic impact of the percentages of SRC in poorly cohesive GA is still a matter of debate and should be urgently studied.

Table 1: Subcategories of poorly cohesive cells carcinoma proposed by the European consensus (PCC: Poorly Cohesive Cells; SRC: Signet Ring Cells; NOS: Not Otherwise Specified)

Category of PCC	**SRC type**: >90% of Signet Ring cells
	PCC with SRC component: <90% but >10% of SRC
	PCC-NOS: <10% of SRC

Japanese classification system (48)

Historically, the Japanese classification system categorized GC into two groups: differentiated and undifferentiated (49). SRC-GC were included in the UND-group. The recent Japanese classification is mainly based on the WHO classification and

distinguishes papillary adenocarcinoma, tubular adenocarcinoma (well- and moderately-differentiated), poorly differentiated adenocarcinoma (solid type and non-solid type), SRCC and MAC (48).

Other classifications less used

Ming's classification (21)

A simple macroscopic and microscopic classification was proposed dividing GC into two types: expanding and infiltrative. Tumor cells in the expanding type grow en masse and by expansion, resulting in the formation of discrete tumor nodules. Tumor cells of the infiltrative type penetrate individually and widely, resulting eventually in diffuse involvement of the stomach.

Goseki's classification (50)

By combining two of the morphological characteristics of GC (i), the degree of differentiation of the glandular tubules and (ii) the amount of mucus in the cytoplasm, the histological type of the GC is categorised into four groups: Group I: well differentiated-poor mucus; Group II: well differentiated-rich mucus; Group III: poor differentiated-poor mucus; Group IV: poor differentiated-rich mucus.

Correlation between classifications

There is a strong correlation between Ming and Laurén's classifications (51,52) in which infiltrative type reflects diffuse type whereas expanding type refers to intestinal type. In regards to Goseki's classification, it was found a strong correlation with WHO, Laurén and conventional grading system of differentiation but not to the Ming classification (42,53). Several studies compared the WHO's and the Laurén's classifications with discordant results regarding the concordance between the two classifications (8,23,54–62) (Table 2). SRC-GC were mainly classified as diffuse type in 66.2% to 96.4% of cases. SRC-GC were classified as mixed type in 2.4% to 26.2% of cases and more rarely as intestinal type in 0% to 7.6% of cases. Although Laurén's classification is widely used, it is impossible to evaluate clinico-pathological and outcome differences according to the proportion of SRC component.

Table 2: Concordance rates between WHO and Laurén's classification. *: Missing data; SRC-GC: gastric cancer with major component of signet ring cells

	SRC-GC according to WHO			
Authors	n	Intestinal	Diffuse	Mixed
Wanebo 1993 (61)	187	2%	87%	11%
Hass 2011 (56)	160	7.6%	66.2%	26.2%
Lee 2012 (58)	320	0.0%	90.6%	9.4%
Heger 2014 (23)	235*	0.0%	75.3%	20.0%
Chon 2016 (54)	1646	1.2%	96.4%	2.4%
Pyo 2016 (59)	3170	0.6%	96.3%	3.1%
Pyo 2016 (60)	5309	0.0%	96.1%	3.9%

Overall the absence of correlation between the classifications renders the analysis of the literature very complex. Stelzner et al proposed a subclassification of the mixed type of GA for a better understanding and interpretation of these tumors (63).

Molecular classifications: the new attrait

Achieving a detailed molecular understanding of the various genomic aberrations associated with GC will be critical to improving patient outcomes. The recent years has seen considerable progress in deciphering the genomic landscape of GC, identifying new molecular components such as *ARID1A* and *RHOA*, cellular pathways, and tissue populations associated with gastric malignancy and progression (64–66). The Cancer Genome Atlas (TCGA) project is a landmark in the molecular characterization of GC (34).

In 2013, Lei and colleagues identified in a relatively large number of primary GC (n=248) three molecular subtypes of GC by using a consensus hierarchical clustering with iterative feature selection: (i) the mesenchymal subtype, associated strongly with the Laurén diffuse-type and consequently SRC-GC, (ii) the proliferative subtype characterized by high levels of genomic instability, *TP53* mutations, and DNA hypomethylation associated strongly with the Laurén intestinal type and (iii) the metabolic subtype. They found notably that patients with metabolic-subtype tumors benefited preferentially from 5-fluorouracil (5-FU) treatment and that mesenchymal-subtype cells resemble cancer stem cells, and, consistent with this resemblance, are preferentially sensitive to PI3K-AKT-mTOR inhibitors (67).

TCGA project proposed, with an analysis of 295 treatment naïve GC, a molecular classification dividing GC into four subtypes (Figure 1) (34):

- Tumors positive for Epstein–Barr virus (EBV) (9%), which display recurrent *PIK3CA* mutations, extreme DNA hypermethylation, and amplification of *JAK2, PD-L1* and *PD-L2.* PD-1 expression within tumor-infiltrating lymphocyte cells is observed in more than half of the EBV-positive GC and immunohistochemical studies revealed high PD-L1 staining in association with high microsatellite instability (MSI-high) and EBV-positive tumors (68).
- Tumors with microsatellite instability (21%), which show elevated mutation rates, including mutations of genes encoding targetable oncogenic signalling proteins; this phenotype is associated with more favorable outcomes (69).
- Genomically stable tumors (20%), which are enriched for the diffuse histological variant (73%) and mutations of *RHOA*, *CDH1* or fusions involving RHO-family GTPase-activating proteins; SRC-GC are consequently mainly included in this molecular category. A separate study highlighted the potential for treatment targets of *RHOA* mutations in diffuse-type GC by identifying non-synonymous mutations in 25.3% of 87 specimens of tumor cells (64).
- Tumors with chromosomal instability (50%), which show marked aneuploidy and amplifications of genes involved in receptor tyrosine kinase/RAS/MAPK signalling.

Identification of these subtypes provides a roadmap for patient stratification and trials of targeted therapies.

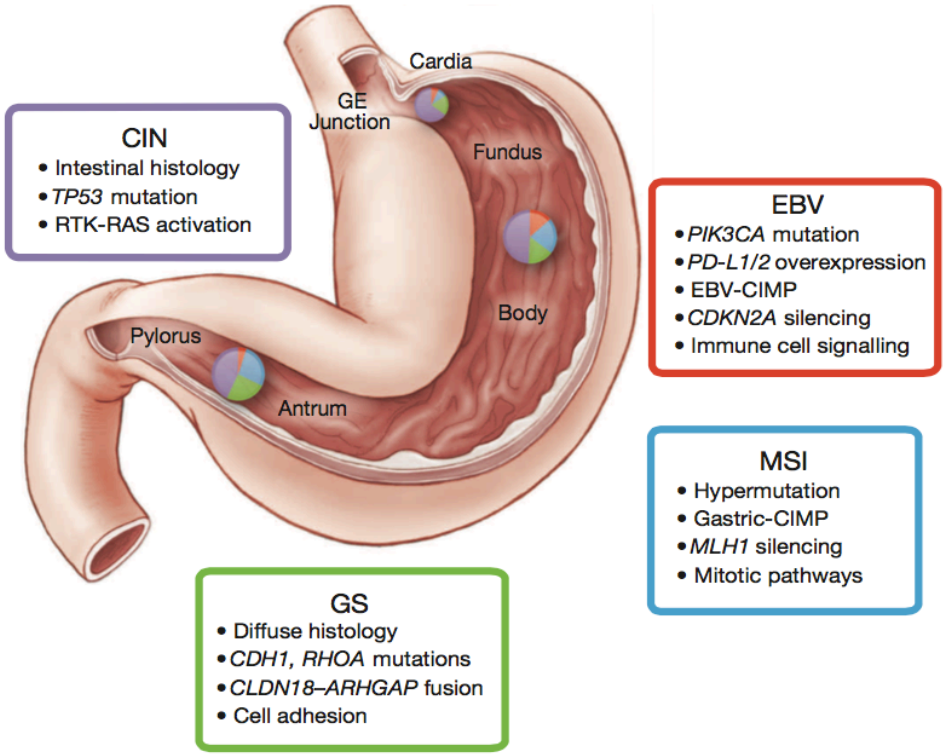

Figure 1: Molecular based classification of gastric cancer according to the Cancer Genome Atlas (34).

More recently, another molecular analysis study of GC (n=300) identified four subgroups of tumors, associated with distinct clinical outcomes among a cohort from the Asian Cancer Research Group (55) :

- Mesenchymal-like type which includes diffuse-subtype tumors and consequently most of SRC-GC has tendency to occur at an earlier age and is associated with the worst prognosis (Hazard ratio (HR)=1,899; p=0,019 in multivariate analysis) and the highest risk of recurrence (63%) of the four subtypes (70). The microenvironment especially in the mesenchymal-like subtype, could offer new therapeutic possibilities (targeting TGF-ß pathway, intra-tumoral stroma or the immunologic cross talk with anti-PD-L1 antibodies).
- Microsatellite-unstable tumors characterized by numerous mutations and corresponding to intestinal-subtype. They occur in the antrum and are associated with the best overall prognosis and the lowest frequency of recurrence (22%) of the four subtypes.
- Tumor protein 53 (*TP53*)-active tumors (the most frequently mutated gene in GC) characterized by more Epstein-Barr virus infection
- *TP53*-inactive tumors reflecting to chromosomal instability subgroup

These two last subtypes include patients with intermediate prognosis and recurrence rates, with the *TP53*-active group showing better prognosis. Thoses results have been

confirmed within 3 distincts cohorts including overall 682 patients.

Key challenges for the future will involve the translation of these molecular findings to clinical utility, by enabling novel strategies for early GC detection, and precision therapies for individual GC patients. In addition to this prognostic impact, molecular classifications have been recently shown to be associated with tumor response to treatment (ie. chemotherapy and immunotherapy) and will probably play a crucial role in treatment decisions for GC allowing individualized treatment in the near future (37,67,71,72).

To conclude, macroscopic histological and more recently molecular classifications of GC individualize a subtype of GC corresponding to SRC-GC. Clearly the analysis of the literature is hampered by the absence of strict correlation between the different classifications. An international consensus would be helpful in order to clarify those discrepancies.

Histological and molecular specific aspects of SRC-GC

The tumor cells of SRC-GC may have different morphologies. In the classical form (presented in figure 2), nuclei push against cell membranes creating a classical signet ring cell appearance due to an expanded, globoid, optically clear cytoplasm. These contain acid mucin and stain with alcian blue at pH 2.5. However certain cells contain little or no mucus and retain a central nucleus with various morphologies such as (i) cells with central nuclei resembling histiocytes, (ii) small, deeply eosinophilic cells with cytoplasmic granules containing neutral mucin; (iii) small cells with little or no mucin, or (iiii) anaplastic cells with little or no mucin (46). These cell types intermingle with one another and constitute varying tumor proportions. The number of malignant cells is comparatively small and desmoplasia is prominent. Interestingly, a multivariate analysis of data from 175 SRC-GC showed the high intratumor stromal proportion as an independent prognostic factor to predict worse disease-free survival (DFS) (HR=2.288; p=0.001) and overall survival (OS) (HR=2.503; p=0.001) (73).

Special stains, including mucin stains (PAS, mucicarmine, or Alcian blue) or immunohistochemical staining with antibodies to cytokeratin, help detect sparsely dispersed tumor cells in the stroma. Cytokeratin immunostaining detects a greater percentage of neoplastic cells than do mucin stains.

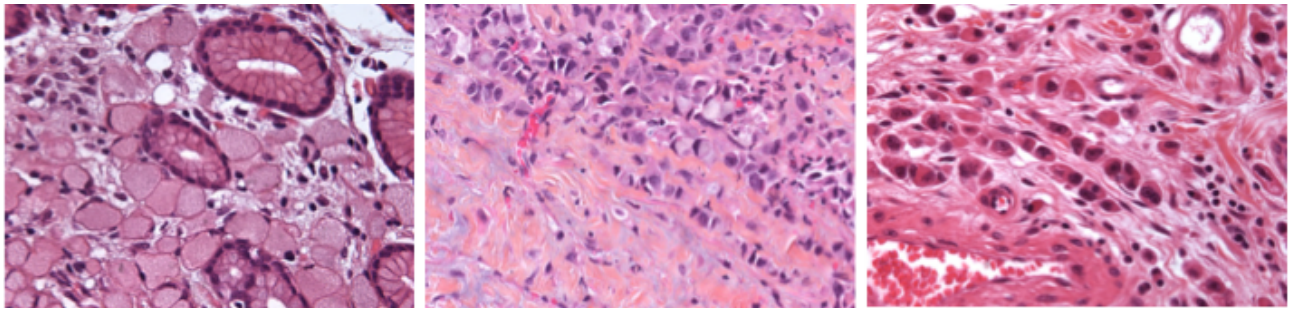

Figure 2: Gastric adenocarcinoma with signet ring cells on microscopic analysis according to Verona's classification 2017. Left image: pur-gastric signet ring cells carcinoma; middle: intermediate SRG-GC; right rimage: poorly-cohesive cells gastric carcinoma not otherwise specified. Images provided by institute of pathology, CHU Lille (F. Renaud).

SRC-GC has a specific oncogenesis that differs from that of tubular GA (74). The two main pathologic processes at a cellular level are loss of cell-cell adhesion molecules and accumulation of mucin in large vacuoles (66,75–77). E-cadherin deficiency has been reported to initiate carcinogenesis in a large proportion of SRC-GC cases, in both familial (through mutation) and sporadic (mostly through promoter hypermethylation or loss of heterozygotie) cases (78,79).

Reduced or abnormal *E-cadherin* expression have also been described in diffuse carcinomas and poorly differentiated (80). *CDH1* is a tumor suppressor gene, which encodes E-cadherin, a transmembrane protein central to cell adhesion. Of note, a recent study showed that *CDH1* somatic epigenetic and structural alterations are as frequent in intestinal (26%) as in diffuse (34%) GC, suggesting histotype independence (79). The reduced expression of *E-cadherin* is strongly associated with the onset of peritoneal carcinomatosis, whereas tumors metastasizing to the liver generally present a normal expression of this molecule. Reduced *E-cadherin* expression has been associated with reduced survival (79,81). Loss of *E-cadherin* function has also been implicated in the pathogenesis of sporadic colorectal and other cancers (82) and some case reports have mentioned colorectal and appendiceal SRCC in *CDH1* mutation carriers (82,83). While *CDH1* mutations seem to be the most frequent abnormality leading to SRC-GC, other adherence molecules could be involved in fewer cases, such as somatic mutations of β-catenin/APC genes or dysregulation of the Wnt/β-catenin pathway (84–86) .

Epidemiology

Incidence increasing

Worldwide, GC ranked fifth for cancer incidence and second for cancer deaths in 2013. For developed countries, it ranked fifth for incidence and third for mortality, and in developing countries, it ranked third for both incidence and mortality (87).

Despite a decrease in the overall incidence of GC in recent decades (because of *Helicobacter Pylori* eradication, increased standards of hygiene, improved food conservation and conscious nutrition), the incidence of SRC-GC is constantly increasing, mainly in the United States and in Europe (1–12,88). Using the Surveillance, Epidemiology, and End Results (SEER) data from 1973 to 2000, Henson et al. reported that rates for the intestinal type decreased by 50%, whereas rates for the diffuse type increased by more than 400% (5).

Ethnicity

The proportion of SRC-GC among GC has been reported, mainly in surgical studies, to vary from 3.4% to 24.6% in Asian studies (6,8,54,57,89–104) and from 8.3% to 50.0% in Western studies (2,13–16,56,61,89,105–110).

Several studies using the SEER database have been published and found a lower incidence of SRC-GC among white people when compared to other ethnicities (11,12,105). Two of those studies underlined the higest frequence of SRC-GC among primarly Asian population when compared to other ethnicities (12,105). Another Western study carried on 2043 patients with less than 10% of Asian patients showed a significant greater proportion of SRC histology among those patients (16 vs 8%, p=0.0006) (111). However, Asian patients living in North America may not be representative of the primarly Asian population suggesting a potential role of the environment or the lifestyle in those variations (112–115).

When looking at the series of early gastric cancer (EGC), the proportion of individualized SRG-GC is higher in Eastern (6,54,90–93,95,96,99–103,116–120) than in Western countries (13,121). This may be explained by the systematic policy of GC screening in Eastern countries. Indeed, SRC-GC tumors show tendencies to be larger and to spread superficially to mucosal and submucosal layers (122), allowing earlier detection and beeing consequently more frequently detectable.

Specific trend in young and female patients

SRC-GC epidemiology and risk factors differ substantially from those of other types of GC. SRC-GC patients have younger age distribution [2,8,11,13,16,28,36,39,54,56,59,90–92,95,96,98,99,101,102,105,106,108,116,117,119,123–129] with a mean age ranging from 55 to 61 years, consistently 7 years before non-SRC-GC (96,102,105) and higher proportion of female (lower male/female ratio) [2,8,11,13,16,28,36,54,56,57,59,90–93,95,96,98–102,105,106,108,116,117,124,125,127–131] compared with other histologic subtypes.

The reason for SRC-GC association with female remains unknown. Several studies have evaluated the association of hormons receptors expression (estrogen receptors (ER), mainly ER-ß or progesteron receptors) with histological type and prognosis with conflicting results regarding both (45,57,132–138).

Risk factors

The vast majority of GC are sporadic and seem to be the results of the cumulative effects of (i) environmental factors such as *Helicobacter Pylori* infection, tobacco, alcohol, dietary habits and (ii) genetic factors associated with minor predisposition (139,140). Besides minor predisposition genetic factors involved in the genesis of sporadic cancers, other genetic factors may play a role in the context of familial aggregations of GC occurring in roughly 10% of cases (141).

Sporadic GC carries wide geographical variations, presumably due to environmental exposure or genetic predisposition. Following migration of Japanese individuals to Hawaii, the rate of intestinal type cancers dropped by 50% indicating causal environmental factors while that of diffuse GC remained similar suggesting a stable hereditary component (142).

While the underlying mechanisms that cause diffuse/SRC-GC remain poorly understood, it is thought to be less related to smoking, alcohol drinking and consumption of fruits and vegetables than glandular/intestinal GC (143–146). Further, the former arises from a multistep genetic carcinogenesis pathway independent of the atrophic gastrointestinal metaplasia-dysplasia sequence that characterizes the latter (143). The role of other risk factors in GC (salt-preserved food, smoking, auto-immune gastritis) or cardia cancer (reflux, obesity) is not well studied in SRC-GC.

Infection with *Helicobacter pylori* leading to chronic gastritis is involved in most cases of non-SRC-GC, with the exception of cardia cancer (favoured by gastroesophageal reflux, obesity and alcohol consumption (4,147). However, the role of *H. pylori* in SRC-GC is more controversial (148). Indeed, since wide eradication of this bacterium, *H. pylori*-negative GC entity has been emerging. This entity may include several subtypes, such as GC of the fundic gland and SRC-GC, thus questioning the role of *H. pylori* in these histologic subtypes (149). In addition, the diffuse type has been correlated with blood group A (146).

Incidence of SRCC type among other digestive carcinomas

Among the 24,171 patients with SRCC recorded in the SEER database, 63.4% had SRC-GC, followed by colon (18.2%), esophagus (5.0%), rectum (3.5%), lung (3.1%), pancreas (1.8%), breast (1.5%), bladder (1.3%), small intestine (1.1%), and gallbladder SRCC locations (1.0%) (150).

Hereditary Diffuse Gastric Cancer (HDGC)

Although most GC are sporadic, approximately 1-3% of GC arise from inherited GC predisposition syndromes and are commonly of the diffuse type (141). Inherited GC comprises at least three major syndromes: HDGC, GA and proximal polyposis of the stomach (GAPPS) (151), and familial intestinal GC (FIGC). Early-onset diffuse gastric cancer (DGC), multi-generational DGC and lobular breast cancer clinically define HDGC.
Clinical criteria for HDGC entity has been first established in 1999 by the International Gastric Cancer Linkage Consortium (IGCLC) (152) then first updated in 2010 (153) and finally updated by a multidisciplinary workshop in 2015 (154), taking into account first-degree and second-degree relatives. Critera for genetic counselling are:

(1) Families with two or more patients with GC at any age, one confirmed DGC,
(2) Individuals with DGC before the age of 40,
(3) Families with diagnoses of both DGC and LBC (one diagnosis before the age of 50),

Further, updated criteria (154) suggest that *CDH1* testing could be considered in patients with :
(4) Bilateral or familial of two or more LBC before the age of 50,
(5) Personal of family history of cleft lip/palate in a patient with DGC,
(6) Presence of precursor lesions for SRCC (in situ SRC and/or pagetoid spread of SRC).

HDGC has been initially genetically explained by germline alterations of *CDH1* leading to an autosomal dominant predisposition to GC (141,155). Aberrant activity of *E-cadherin* leads to abnormal morphology, growth patterns and invasion by SRCs in HDGC (80). Using initial criteria, 30 to 50% of individuals with HDGC have an identified germline mutation in *CDH1* (156–158). A recent study found that only 34 of 183 index cases (19%) who met current IGCLC criteria were found to have germline pathogenic *CDH1*-mutations (159). Among HDGC without identified germline mutation, more than 50% carried *CDH1* somatic alterations (promoter hypermethylation exclusively) (79). In addition, in *CDH1* mutation–negative index cases, candidate mutations were identified in 16 of 144 probands (11%), including mutations within genes of high and moderate penetrance: *CTNNA1*, *BRCA2*, *STK11*, *SDHB*, *PRSS1*, *ATM*, *MSR1*, and *PALB2*. The authors suggested that In HDGC families lacking *CDH1* mutations, testing of *CTNNA1* and other tumor suppressor genes should be considered (159).

From the histological point of view, one to > 100 small foci of SRC-GC are found in the stomachs of nearly all mutation carriers (41,160–162). In a series of 41 asymptomatic *CDH1* mutation carriers with no evidence of tumor on preoperative work-up, histopathological examination of prophylactic total gastrectomy (PTG) specimens identified one macroscopically invisible or more foci of intramucosal SRCC in 35 of them (85%) (163). This is in accordance with a previous study carried out on 23 *CDH1* mutation carriers where preoperative endoscopy and mucosal biopsies revealed the disease in only 2 patients (9%) and final standardized pathological evaluation of total gastrectomy specimens showed evidence of SRCC in 22 of 23 (96%) patients (164). Although the clinical significance of such foci is not clear, it is recommended to consider PTG in all mutation carriers (154).

Two distinct types of intraepithelial lesions have been identified as precursors of invasive cancers in *CDH1* mutation carriers and have been included in the recent diagnostic criteria of HDGC (41,141) :

- in-situ SRC corresponds to the presence of SRC, generally with hyperchromatic and depolarised nuclei, within the basal membrane,
- and pagetoid spread of SRC below the preserved epithelium of glands or foveolae.

Estimated life-time risk of GC in carriers of a *CDH1* mutation varie according to studies (153,156,158,159). Initial data suggested that *CDH1* mutation carriers by the age of 80 had (i) a more than 80% risk of developing DGC in both men and women and (ii) a 60% risk of developing LBC in women (153). More recently, a study reported, by the age of 80 years, a cumulative incidence of DGC of 70% (95% CI, 59%-80%) for males and 56%

(95% CI, 44%-69%) for females, and a risk of LBC for females of 42% (95% CI, 23%-68%) (159).

Advanced HDGC predominantly presents as linitis plastica with diffuse infiltration of the gastric wall. Histology can show mainly or exclusively SRC. However, more often these tumors are composed of a pleomorphic neoplastic infiltrate with a small subset of or without classic SRC. From the histological point of view, advanced GC of *CDH1* mutation carriers do not have any specific characteristics when compared to sporadic DGC (SDGC) (141). However, a recent study evaluated the immunohistological differences between HDGC and SDGC and revealed that all HDGC (n=23) were negatives for *CDX2* while 19 of 20 SDGCs were positives, suggesting that HDGC may develop along a different carcinogenetic pathway from SDGC (165).

Linitis plastica / Borrmann type IV GC / Scirrhous GC

Definition

Linitis plastica (LP) is macroscopically described as an increase thickening and rigidity of the gastric walls with an aspect of linen. On a histological point of view, it corresponds to an involvment of the entire stomach wall by carcinoma cells, mostly SRC, with a very abundant sclerous stroma. LP is an uncommon variant of GC occuring in 7–17.4 % of cases (89,126,129,166–171,171–177). LP incidence may even be higher in stage IV GC (25%) (178).

LP is rarely individualised in studies for two main reasons; (i) some authors confuse the histological and macroscopical definition (179–181) assimilating SRC-GC with LP, thus adding to confusion and (ii) LP is also referred to as Borrmann type IV or scirrhous gastric carcinoma (SGC).

Borrmann classification is a macroscopic definition of advanced GC (182), Borrmann type IV corresponding to a macroscopic diffusely infltrative tumor. The macroscopic characteristics of SGC include a grossly thickened and hard wall tumor without marked ulceration or raised margins. This type is categorised as Borrmann type IV. The common microscopic features of SGC show that undifferentiated cancer cells or SRC proliferate with abundant fibroblasts (183). In contrast to most GC, SGC cells do not form glands (184). The histopathological feature is cellular spread to the submucosa and stroma with minimal mucosal alterations that impeding detection at an early stage, accompanied by an excessive desmoplastic reaction (185). Because most Borrmann type

IV tumors are of the undifferentiated type, these are often clinically regarded as almost equal to SGC. SGC is also called diffusely infiltrating carcinoma, LP or leather bottle type. The definitions of these names slightly differ from each other; however, its clinicopathological features are almost the same (183,186). An illustration of gastric LP is presented in figure 3.

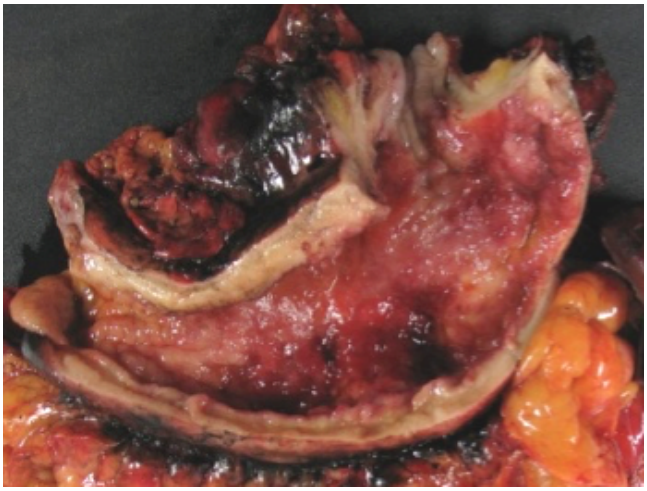

Figure 3: Photo of a gastric linitis plastica.

Photo provided by institute of pathology, CHU Lille (F. Renaud).

Several studies showed an equivalence between SRC-GC and Borrmann type IV or LP GC (16,92,93,95,97,101,104,146,166,187). In a study carried out at our center, among a population of 159 resected patients for SRC and non-SRC-GC, LP occured in 35.6% in the SRC group versus 6% in the non SRCC group ($p<0.001$) (15). Most of LP in the non SRC-group had a minor component of SRC. That is to say that LP and SRCC are not synonyms (188) but are however closely associated.

Characteristics and prognosis of LP

The most common sites of gastric LP are the antral and pyloric regions (whereas proximal spread towards the gastric body can vary). The fundus is least often involved (176,185,189). Young female patients are more often concerned by LP (126,166,174,175,177,189,190). In patients with LP, peritoneal carcinomatosis (PC) occurres commonly and regardless of the nodal status (173). Conversely, liver metastasis are unfrequent at the time of diagnostic (174,177). Most of the studies conclude to an unfavorable prognosis for LP when compared to other GC [126,166,167,169,174,175,187,188,191–197]. Concordantely, Borrmann type IV GC is associated with more advanced tumor stage

(166,167,169,172,174,175,177,188,189,194,195,198,199), higher risk of lymph node involvement (166,167,169,172–177,189,192,194,195,197,199,200) and PC (167,169,172–177,188,192,194,200–202), higher rate of microscopic disease at the resection margins (166,167,169,170,172,173,176,177,185,193,195,196,199,203) and is frequently found as an independent prognostic factor (166,174,177,188,189,195,196,204,205). In a case-matched study comparing SRC and non-SRC resected tumors published by our group, SRCC type but not LP was an independent prognostic factor (15). In another Western study, LP was found as an independent factor of poor OS in the SRC-GC subgroup ($p>0.02$, n=899) but not in the non-SRC-GC-group ($p<0.867$, n=900) (129). Overall, LP carries a dismal median survival, ranging from 6 to 12 months, and 5-year survival between 8 and 13 % (173,176,196,199,200,206).

Early recurrence is common (170). Peritoneal dissemination is the main site of recurrence even after curative surgery (170,172,173,176,177,199,207,208). A study performed on 424 patients with esophageal and SRC-GC who benefited of curative surgery showed that LP was an independant risk factor of PC recurrence for SRCC histological subtype (OR=4.8, $p<0.001$) (207). This is in accordance with a previous study which showed Borrmann type IV (n=47) as an independent predictor of peritoneal dissemination after curative surgery (208).

Role of surgery in LP

The diagnosis of LP carries significant controversy regarding its surgical management since curative resection is obtained roughly in equal or less than half of patients (169,172–177,188,196,199,209,210). Despite higher rates of total gastrectomy when compared to non-LP patients ($p<0.01$), LP patients showed a higher rate of R1 resection (167,195). This can be explained by the ability of those cells to spread either continuously with the primary lesion or discontinuously from it, forming skip submucosal foci (102).

A recent meta-analyse regrouping the results of fifteen studies concluded that resection of LP was beneficial when compared to an absence of resection, even if it was not curative (194). This remains highly discussed since several studies found no improvement in survival between R1, R2, and unresected gastric LP patients highlighting the importance of a complete surgical resection (173,176,193,209).

Except in a small size study (170), most authors underline the relevant benefit of a curative R0 surgery in LP (126,172,173,176,185,191,193,198–200,210–213), with R0

surgery as an independant favorable prognostic factor (166,171,174,175,200,210). Two studies suggested that R0 resection of a stage III LP or of a Borrmann IV GC was associated with a same prognosis as a stage III GC with no-LP or as a pT4B other type of GC (167,189). Even in case of necessity of multivisceral resection, patients with LP have been showed to benefit from a significant survival improvement (176).

Further studies should be accomplished in order to better characterize LP among SRC-GC and to determine whether a specific management should be proposed especially to limit the risk of PC recurrence.

Prognosis

Differences according to the stage of the disease

Most studies agree on the poor prognosis of diffuse GC according to Laurén's classification (3,20,27–31,36,40,52,56,61,126,128,143,214–222). SRC-GC have likewise been associated with a dismal prognosis [8,15,16,22,23,29,56,94,98,108,129,178,207,214,223,224], with however more conflicted data [3,6,32,53,54,58,91,92,94,95,101–103,105,106,111,119,125,187,225–231].

Prognostic role of SRC-GC may depend on the stage of the cancer at the time of treatment [3,13,54,90–92,94–96,99–103,119,121,125,129,227].

EGC has been described by the Japanese Society of Gastroenterological Endoscopy in 1962 as GC not extending beyond the submucosa (pT1a or pT1b) regardless the lymph node status whereas advanced gastric cancer (AGC) is defined as depth of invasion exceeding submucosa (232). Data in the literature regarding AGC mostly originate from Western series (11,13,15,16,23,28,36,40,56,98,105,109). In those series, few EGC are sometimes mixed with AGC. Data regarding EGC mostly originate from Eastern series owing to a higher incidence of the diseases with consequently a policy of systematic screening. Table 4 summarizes studies reporting prognostic value regardless of the stage of SRC-GC.

Numerous reports from Western countries, do identify SRC-GC as a predictor of poor prognosis (90,91,95,99,100,103,116,125). Conversely, numerous reports from Eastern countries, do not identify SRC-GC as a predictor of poor prognosis (90,91,95,99,100,103,116,125).

Table 4: Summary of studies reporting prognostic value of SRC-GC all stages confounded. GC: gastric cancer; LNM: lymph node metastasis; SRC-GC: gastric cancer with signet ring cells; NSRC-GC: gastric cancer other types ; WMD : well-and moderatly-differentiated gastric cancer ; PD : poorly differentiated gastric cancer ; MC : mucinous cancer ; NS : non significant ; * The survival rate of patients with stage IV SRC-GC was poorer than those with the other three types.

Global GC	n	n SRC-GC/%	% LNM	5-y survivale rate % (SRC vs other)	Univariate	Multivariate	Compared to
Eastern studies							
Maehara 1992 (99)	1500	51/3.4	33.3	74.5 vs 52.4	p<0.01	-	NSRC-GC
Kim 1994 (93)	3702	450/12.2	50.6	59.7 vs 57.7/48.6/43.1	NS	-	WD/MD/PD
Otsuji 1998 (100)	1498	154/10.3	27.9	68.2 vs 43.9 (10-y survival rate)	p<0.05	-	NSRC-GC
Yokota 1998 (102)	923	93/10.1	43	worse	NS	-	NSRC-GC
Kim 2004 (119)	2358	204/8.7	26.5	60.2 vs 48.9	p<0.01	NS	NSRC-GC
Park 2008(101)	2275	251/11.0	46.2	66.2 vs 66.7/54.5/51.0	WD: NS ; PD/MC :p<0.001	p=0.002*	WD/PD/MC
Zhang 2010 (103)	1439	218/15.1	76.1	44.9 vs 36	p=0.013	NS	NSRC-GC
Chiu 2011 (90)	2439	505/20.7	53.7	57.6 vs 56	NS	-	NSRC-GC
Jiang 2011 (92)	1439	211/14.7	52,0	49.8 vs 41.4	p=0.001	-	NSRC-GC
Lee 2012 (58)	1002	320/31.9	37.2	84.8 vs 71.9/57.8	p<0.001	NS	PD/MC
Kwon 2014 (96)	769	108/14.0	43.5	55.4 vs 64.5/46.2 (10-y survival rate)	p<0.001	NS	WD-MD/PD-MC
Liu 2015 (98)	1464	138/9.4	30.4	36.2 vs 49.5	p<0.001	p<0.001	NSRC-GC
Chon 2016 (54)	7667	1646/21.5	25.8	80.0 vs 70.0 (10-y survival rate)	p<0.001	NS	WMD/PD
Lu 2016 (8)	2199	354/16.1	-	15.9 vs 22.1 months	p=0.002	<0.001	NSRC-GC
Western studies							
Theuer 1999 (106)	3020	453/15.0	NR	similar	NS	NS	NSRC-GC
Piessen 2009 (15)	180	59/32.8	83.1	28 vs 46	p=0.004	p=0.004	NSRC-GC
Taghavi 2012 (105)	10246	2666/26	59.7	similar (Disease-specific survival)	NS	p=0.15	NSRC-GC
Bamboat 2014 (13)	569	210/36.9	61.0	49 vs 24/43 (5-y cumulative-mortality)	p<0.0001	-	WMD/PD
Postlewait 2015 (16)	768	312/40.6	66.3	33.7 vs. 46.6 months (OS)	p=0.011	NS	NSRC-GC
Voron 2015 (109)	1799	899/50	73.2	26 vs 51 months (median survival)	p<0.001	p<0.041	NSRC-GC

Advanced gastric cancers (AGC)

Table 5 presents studies reporting prognostic value specifically in AGC. At advanced stage, when compared to non-SRC-GC, SRC-GC are associated with a lesser sensitivity to chemotherapy (14,108,129), present more advanced stage (123), deeper tumor invasion (92,97), a potential to infiltrate the gastric wall with a higher proportion of Borrmann type IV tumor (92,95,97,104,123,125,146,214), a greater risk of metastatic

disease (105) with more specifically PC (15,92,93,97,100,109) and lower rate of R0 resection due to inflitrative characteristics with a higher risk of involvment of longitudinal margins (15,16,23,97,109,233), a higher incidence of lymph node metastases (LNM) (13,15,36,93,97,105,109,119,123,214), and earlier and more frequent disease recurrence (15). In AGC, the prognosis of SRCC is commonly thought to be poor (13,15,23,54,90,93,97,101,102,104,125,227) in Western countries.

In several Eastern studies, patients with SRC-AGC had a similar (92,95,99,100,102,106,119) or poorer (54,90,93,96,97,104,125) prognosis than non-SRC-GC. Results remain however conflicting and a recent population-based study in the United States demonstrated that after adjusting for stage, SRC-GC did not necessarily portend a worse prognosis (105). This finding is supported by results from several studies in which SRCC had a worse prognosis in univariate analysis, but not in multivariate analysis, after adjustment for tumor stage (16,23,92,96,97,104,108,126,219,223,230,234,235).

However, due to stage differences between SRC and non-SRC-GC, a simple a posteriori adjustment by multivariable analysis could impair interpretation of the results. Given that randomized comparison cannot be performed, a matched case control study seems to be the method of choice for small cohorts to control prognostic variables that are strongly linked to SRC, with the use of a multivariable analysis to identify prognostic factors on the basis of comparable SRC and non-SRC populations (236). This point had been taken into account in a case-matched study with matching on pTNM stage. Despite this matching, SRC-GC portented a worst prognosis in multivariate analysis (15). Several reports have concordantely identified SRC-GC as an independent predictor of poor prognosis (8,15,98,129,178), especially in Western countries.

In conclusion, the prognosis impact of SRC in AGC, has been mostly associated with bad prognosis but this remains controversial, in both Western and Eastern studies.

Table 5: Summary of studies reporting prognostic value of SRC-GC at advanced stage. AGC: advanced gastric cancer; LNM: lymph node metastasis; SRC-GC: gastric cancer with signet ring cells; NSRC-GC: gastric cancer other types ; WMD : well-and moderatly-differentiated gastric cancer ; PD : poorly differentiated gastric cancer ; MC : mucinous cancer ; NS : non significant

AGC	n	n SRC/%	% LNM	5-y survivale rate % (SRC vs other)	Univariate	Multivariate	Compared to
Eastern studies							
Maehara 1992 (99)	1116	23/2.1	60.8	42.5 vs 37.6	NS	-	NSRC
Kim 1994 (93)	2917	265/9.1	80.8	33 vs 45.4/38.8/35.3	p<0.05	-	WD/MD/PD
Otsuji 1998 (100)	930	60/6.4	63.3	44.4 vs 27.5 (10-y survival rate)	NS	-	NSRC
Yokota 1998 (102)	430	52/12.1	-	worse	NS	-	NSRC
Kunisaki 2004 (95)	600	54/9.0	57.4	Similar	NS	-	NSRC
Kim 2004 (119)	1797	110/6.1	47.3	35.1 vs 39.5	NS	-	NSRC
Li 2007 (97)	4759	662/13.9	75.7	42.4 vs 50.1	0.009	NS	NSRC
Chiu 2011 (90)	1860	356/19.1	71.6	41.5 vs 46.3	p=0.018	-	NSRC
Jiang 2011 (92)	2046	157/7.7	64.3	31.5 vs. 35.7	NS	NS	NSRC
Zu 2014 (104)	741	44/5.9	56.8	43.4 vs 87.1/57.1/50.6/62.7	p=0.012	0.028	WD/MD/PD/MC
Kwon 2014 (96)	443	57/12.9	73.7	26.0 vs 50.5/38.4 (10-y survival rate)	p=0.044	NS	WD-MD/PD-MC
Chon 2016 (54)	1777	555/31.2	-	53 vs 58/52 (10-y survival rate)	p<0.001	p<0.001	WMD/PD
Western studies							
Heger.2014 (23)	723	235/32.5	63.0	26.3 vs 46.6 months (median survival)	p<0.001	p=0.02 (backward analysis)	NSRC

Early gastric cancers (EGC)

Studies reporting pronostic value of SRC-EGC are representated in table 6. The prognosis of SRC EGC has been reported in most studies as equivalent to [93,94,96,99,101–103,105,118,119,121] or even better [13,90–92,95,100,116,117,120,125,129,227,237] than non-SRC-GC. The largest study published on 3272 EGC showed that prognosis of SRC-GC was better than well- and moderately-differentiated EGC (HR=0.66, p=0.041 for OS) (54). However, in most of those studies, SRC-GC were more frequently limited to the mucosa [54,62,90,91,93,116,117,123,125,130,237,238] and had fewer LNM [90,91,93,116,119,120,125] than non-SRC EGC. This remains however conflicting since other groups have reported no significant difference between SRC and non-SRC EGC with regard to the depth of invasion and LNM (92,95,96,121). Kim et al. even reported that SRC-EGC had an unfavorable risk of LNM compared to WMD in mucosal cancer (118). Similarly, a Western study found that submucosal involvement was more frequent in the SRC-EGC group (94% vs 85%; p=0.013) (121). However, in this study the authors reported a 5-year OS benefit in SRC-

GC patients (85% vs 76%, respectively; p=0.035). However, this was no more evident when considering exclusively disease-specific survival in multivariable analysis which was similar between groups. Thus, the lower rate of non–cancer-related deaths in the SRC group may be related to younger age (121).

To conclude, SRC EGC seem to be associated with good oncological outcomes, especially in the East whereas more data are needed to better characterize the influence of SRC histology at early stages in Western countries.

Table 6: Summary of studies reporting prognostic value of SRC-GC at early stage. EGC: early gastric cancer; LNM: lymph node metastasis; SRC-GC: gastric cancer with signet ring cells; NSRC-GC: gastric cancer other types ; WMD : well-and moderatly-differentiated gastric cancer ; PD : poorly differentiated gastric cancer ; MC : mucinous cancer ; NS : non significant

EGC	n	n SRC/%	% LNM	5-y survivale rate % (SRC vs other)	Univariate	Multivariate	Compared to
Eastern studies							
Maehara 1992 (99)	384	28/7.3	10.7	100 vs 94.8	NS	-	NSRC
Kim 1994 (93)	785	185/23.6	7.6	92.9 vs 83.9/87.3/93.6	NS	-	WD/MD/PD
Otsuji 1998 (100)	568	94/16.5	5.3	93 vs 76.3	p<0.05	-	NSRC
Yokota 1998 (102)	253	41/16.2	-	Similar	NS	-	NSRC
Hyung 2002 (91)	933	263/28.2	5.7	94.2 vs 91.6	p=0.01	-	NSRC
Kim 2004 (119)	561	94/16.8	2.1	96.3 vs 90.8	NS	NS	NSRC
Kunisaki 2004 (95)	513	120/23.4	9.2	Better	p=0.033	p=0.036	NSRC
Ha 2008 (116)	1520	388/25.5	9.5	99.7 vs 99.1/97.2	NS/p=0.019	-	WMD-PA/PD-MC
Zhang 2010 (103)	138	49/35.5	-	Similar	NS	-	NSRC
Chiu 2011 (90)	579	149/25.7	10.7	96.1 vs 89.6	p=0.01	-	NSRC
Jiang 2011 (92)	269	54/20.1	16.7	94.3 vs 90.6	p=0.007	p=0.011	NSRC
Kwon 2014 (96)	326	51/15.6	9.8	84.0 vs 76.0/65.7 (10-y survival rate)	NS	-	WD-MD/PD-MC
Kim 2014 (118)	2085	345/16.5	9.0%	Similar (disease-related survival)	NS	-	WD/MD/PD
Wang 2015 (120)	334	115/34.4	8.5	93.9 vs 85.8	p=0.027	0.001	UD
Chon 2016 (54)	3272	1091/33.3	-	95 vs 85 (10-y survival rate)	p<0.001	p=0.041 (WMD)	WMD-PD
Imamura 2016 (117)	746	152/20.4	2.0	97.4 vs 89.9	p=0.012	p=0.038	NSRC
Western studies							
Gronnier 2013 (121)	421	104/24.7	24,0	85 vs 76	p=0.035	NS	NSRC
Bamboat 2014 (13)	437	174/39.8	-	0 vs 8/24 (5- disease-specific mortality)	p=0.001	-	WMD/PD

Hypothesis proposed

Several hypotheses may explain those results.

Prognostic role of SRC-GC may depend on the stage of the cancer at the time of treatment (3,13,54,90–92,94–96,99–103,119,121,125,129,227).

The underlying causes for the opposite prognosis for patients with early and advanced GC with SRC histology remain consequently uncertain. Those geographical differences complicate further the analysis of the results since molecular tumor characteristics may differ between continents (113).

Early and advanced SRC-GC may represent 2 distinct subsets with distinct implications (74). Hypothetically, early SRC is associated with low aggressiveness (latent stage) because of a *CDH1* mutation as already reported (153). As a possible explanation, in the setting of HDGC, intramucosal lesions present with an “indolent” phenotype without immunoexpression of Ki-67 and p53 and morphologically characterized by typical signet ring cells, while advanced carcinomas that display an “aggressive” phenotype are composed of pleomorphic cells which are immunoreactive for Ki-67 and p53 (239). When SRC have invaded the muscularis propria, an accelerated tumor process leads to diffuse tumor invasiveness, associated with a greater risk of spread to lymph nodes and peritoneal surfaces and is linked to poor chemosensitivity and prognosis.

Recurrence

GC has the highest risk of peritoneal recurrence among digestive cancers. After curative surgery, the fisrt reason for treatment failure is peritoneal recurrence (240) occuring in approximately half of the cases, despite extensive surgery including D2 lymph node dissection (15,241–247). The two main risk factors of recurrence are LNM and serosal invasion (243,245,247–251). Histological type has been showed to be a significant predictor of recurrence (after excluding patients with LNM) (27) and to predict recurrence location (35).

SRCC has been reported to be an independent favorable predictor of recurrence in EGC (54). Studies on recurrence consequently mostly concern AGC series. Undifferentiated GC (vs. differentiated) (252) and diffuse (vs. intestinal) (23,27,35,218,227,241,253–256) have a higher risk of recurrence (65% vs. 41%, $p<0.0001$ (218)) occuring more frequently on the peritoneum (34% vs. 9%, $p<0.0001$ (218)). On the

contrary haematogeneous dissemination and local recurrence are less frequent is those histological subtypes.

On a concordant way, SRC-AGC (vs. non-SRC-AGC), have a higher risk of recurrence, except for Heger et al. (23,56,109), occuring earlier (3 months earlier in median) (15,16,56,94) and more frequently on the peritoneum (15,23,101,102,257,258). Of note, even in the Eastern literature, similar findings were reported in SRC-AGC regarding recurrence risk (54) and peritoneal seeding (in the subgroup of T3/T4 patients with neural invasion (258). Similar findings were observed when studying the recurrence pattern of tumors using the recent molecular classification published by Cristescu (55).

Diffuse, SRC and undifferentiated histological subtypes are though to disseminate trans-serosally to the peritoneum (243). The higher rate of peritoneal seeding and positive pertioneal cytology at the time of resection may partly explain this short time to recurrence and those higher rates of PC recurrences (15,259,260).

Specificities of SRC-GC progression

Intestinal GC has greater proliferative activity in superficial layers than in deeper ones, whereas in diffuse GC, proliferation is increased in deeper layers and in tumors infiltrating the serosa, resulting in a greater tendency for peritoneal seeding (261). Because of this infiltrating nature, SRC-GC cause few clinical symptoms and are therefore often discovered at an advanced stage which may biase the analysis regarding prognostic impact as previously discussed (13,15,16,40,56,98,105,109). In addition, SRC-AGC are more likely to be found with PC (15,97,100,108,119,125,202,207) or positive pertioneal cytology (259,260) at the time of resection. Peritoneal seeding is frequently unexpected on preoperative CT-scan, and was found in operable patients in 18.6% at explorative surgery in SRC-GC (15). Similar findings have been reported for diffuse (vs. intestinal) (218) and undifferentiated (vs. differentiated) GC (260). A recent meta-analysis regrouping 19 studies (n=35947 patients) showed a less frequent risk of hematogenous metastasis (OR: 0.41, $p<0.001$) for SRC histologic subtype compared to non-SRC (125).

Few studies evaluated specifically specificities of tumor progression in metastatic SRCC patients (15,262). In Piessen et al. study, among non-resected patients, SRC histologic subtype was associated with marginally non-significant higher rates of PC (90.1% vs. 65.2%, $p=0.053$) and neoplastic ascitis (63.6% vs. 34.7%, $p=0.059$) when compared with non-SRC GC (15). A study carried out on 173 autopsy cases of GC in which the primary tumor had not been resected assessed patterns of metastasis.

Interestingly the type of metastatic involvment differed with location and tumor histology. GC of glandular type (ie mainly non-SRCC) showed preferential metastasis to the liver, whereas the non-glandular type (ie mainly SRCC) showed a preference for peritoneal involvement and LNM. Peritoneal involvement was more frequent in younger patients for both types, whereas no differences were observed for liver metastasis (262).

Pre-therapeutic evaluation

General considerations

Due to the specific characteristics of SRC-GC detailed previously, pretherapeutic evaluation should be adapted. Attention should be payed to familial history, with a strict evaluation of clinical criteria of HDGC in order to propose genetic conselling when appropriate. Due to the particular cellular spread in the deeper layer of the stomach with minimal mucosal alteration, especially in LP, endoscopy and superficial biopsies may miss the diagnosis causing delay in treatment. In case of clinical suspicion of SRC-GC, repeated endoscopies should be proposed in association with echography ultrasoud sonography to perform guided and deep biopsies. CT-scan may help showing an increased wall thickness of the stomach and staging laparoscopy looking for infraradiological PC.

Difficulties for histological diagnosis of SRCC

SRCC is one of the few malignant tumors that is likely to be missed on microscopic examination because (i) it could be misinterpreted initially as some type of benign process such as an aggregate of histocytes or a cohesive cluster of pyloric cells with glassy cytoplasm (99), (ii) of a low amount of tumor cells and (iii) proliferation of SRC happens mainly in the submucosa and the quality of biopsies requires deeper sample than usual. Early stages of the disease can be easily missed when using regular hematoxylin and eosin staining because GC hidden beneath the intact mucosal surface epithelium is rarely discovered. Not only is the diagnosis incidental in the early stages, but usually, it is also unexpected (102). In addition, there are benign pseudo-signet ring cells that can mimic signet ring cell carcinoma. Secondly, there are SRCs, which are located within the tubular

structures, so called in situ SRC, which are classified as malignant cells despite the fact that the basement membrane is still intact.

Currently there are no specific immuno-histochemistry markers for routine use. However, histochemical staining (PAS after diastase e.g. mucin staining) and cytokeratin immunostaining help to confirm the presence of signet ring cells.

Reliability of pretherapeutic biopsies compared to definitive specimen histology

Since SRCC is currently defined according to the WHO 2010 classification as a subtype of PCC composed predominantly exclusively of tumor cells with prominent cytoplasmic mucin and a crescent-shaped nucleus eccentrically placed (19), it si questionable whether pretherapeutic biopsies can accuratly predict the diagnosis. In a retrospective study among 254 patients, we showed that presence of SRC in samples obtained from routine pretreatment endoscopic biopsies accurately predicts SRC histology and poor prognosis (sensitivity: 88.1%, specificity: 95.4%, positive predictive value: 92.7%, negative predictive value: 92.4%, and overall accuracy of 92.5%) (127). Among false-negative and false-positive cases, several patients had a minor tumoral component in the surgical specimen. Those cases may be attributed to sampling error due to the limited amount of the tissue to be examined from the pretherapeutic biopsies. Because of the importance of an accurate diagnosis we suggest reassessing biopsy diagnoses in cases of diffuse-type or undifferentiated tumors reported for pretherapeutic biopsy specimens, especially in patients under the age of 50. Except a previous study suggesting a relatively low concordance rate between biopsies and surgical specimen (65-75%) among 100 GC (43), our results are in accordance with several other previous studies (1,2,52,263–266) and therefore suggest that the potential changes in treatment strategy for SRC-GC can be envisaged from biopsies results. New studies are to be performed using the new consensus proposed by the European Chapter of the International Gastric Cancer Association (Mariette et al. Gastric Cancer submitted) (see table 1).

Positron emission tomography

Positron emission tomography (PET) imaging using fluoro-2-deoxy-D-glucose (FDG) may be used for preoperative staging (267) and for the monitoring of postoperative tumor recurrence in GC (268). Care should be taken when using PET FDG in SRC-GC.

SRC-GC has been shown to have a lower PET sensitivity and a lower standard uptake value (SUV) than those of non-SRC-GC (266,269–271). Shah et al. using gene set analysis confirmed that diffuse GC were commonly FDG non-avid (272). However, a study assessing the clinical implication of FDG-PET in SRC AGC found a correlation between a high SUVmax and a more aggresive behaviour with advanced TNM stage and shorter relapse-free survival (273). Overall PET-FDG may be useful in SRCC especially in advanced disease to eliminate distant metastasis, but clinicians should be aware that some SRCC are FDG non-avid.

Staging laparoscopy

Peritoneal dissemination from GC is common and occurs in 5–20% of patients being explored for potentially curative resection with a significant higher risk for SRC-GC vs. non-SRC-GC (18.6 vs 6% in our. series) (15,246,274).

Since the sensitivity of conventional morphological exams (endoscopic ultrasonography or CT-scan) has been shown to be poor to detect peritoneal dissemination, staging laparoscopy is a major tool (275) and should be performed before initiating any treatment.

In addition to a complete and systematic exploration of the abdominal cavity, a peritoneal lavage cytology should be done because it classifies GC as stage IV and it has been showed to be associated with a dismal prognosis, questioning the benefit of an operation (168,176,193) especially in the context of SGC (168,188,193).

Staging laparoscopy is recommended regardless of histological type for GC from stage IB by the European Society for Medical Oncology (ESMO) (276) and even from stage T1b by National Comprehensive Cancer Network (277) and several authors underlined the importance of this recommendation in SRC-GC (15,277–280). New procedures are being evaluated and proposed like laparo-endoscopic single site surgery to improve PC staging, since PC may be difficult to see especially on the mesenteric side of the small intestine (281,282).

Curative intents treatment

Endoscopic resection

Generalities

Endoscopic resection (ER) is accepted as a standard treatment for EGC without LNM. ER is associated with favorable long term outcomes, with minimal invasiveness and satisfactory functional preservation of the stomach, and postoperative quality of life (283–286). Endoscopic mucosal resection (EMR) and more recently endoscopic submucosal dissection (ESD), which enables more complete and extensive en-bloc resection (287) are the two techniques used for ER. ER does not assess the presence of LNM, which is considered as one of the most significant prognostic factors for OS, DFS and recurrence in patients with EGC (288,289). Identification of LNM with CT-scan or endoscopic ultrasonography is unreliable and consequently should be evaluated according to histological parameters of ER (290,291).

Differentiation

The application of ER has first been limited to differentiated EGC (285,292–294) because of the higher risk of LNM associated with undifferentiated (UND) EGC (295–297). In mucosal EGC, LNM risk in differentiated type varies between 0.4% to 1.8% (59,288,296,298) versus 2.9% to 7.3% in UND-type (59,283,292,296,299,300). The safety of the endoscopic approach in mucosal UND-EGC has however been evaluated. UND-GC consist in several histological categories: poorly differentiated, mucinous and SRC types, rendering the analyis of the literature complex.

A South Korean study compared ESD (n=111) vs. surgery (n=382) in patients with intramucosal UD-EGC, through a 1-1 propensity score-matched (n=81). In both groups, two-thirds of the UD-EGCs had SRC type histology. DFS was significantly shorter in the ESD group, but OS was not different between the two groups. The authors concluded that ESD might be a complementary option for the treatment of UD-EGCs, especially in those with SRC-type histology based on strict selection. Nonetheless, close endoscopic surveillance is required because of a high incidence of local recurrence (301).

SRCC may have a unique biologic nature and more favorable features than other UND-EGC types (302) and has been reported to be an independant predictive factor of negative LNM (91).

Parameters to consider ER in SRC-EGC

Histological parameters: Lympho-vascular-invasion and depth of invasion of the gastric wall (mucosal/sub-mucosal spreading)

The most important independent risk factor of LNM is lymphovascular invasion (LVI) by tumor cells (58,116,124,238,288,296,297,299,300,302–308) followed by depth of invasion (58,60,124,130,238,288,297,303,305,306,308–311). A worldwild meta-analysis perfomed in 2017 showed more mucosal invasion (OR: 1.68, 95% CI: 1.24-2.29, p=0.001), and marginally less LNM (OR: 0.68, 95% CI: 0.46-1.01, p=0.054) with SRC EGC compared to non-SRC EGC (125).

Series reporting risk of LNM according to depth on invasion in SRC EGC are presented in table 7. Incidence of LNM in SRC EGC ranged from 2.0% to 16.6% in Eastern studies (90–93,95,96,99,100,116–120,124,130,237,238,283,299,302,303,306–308,311–315) and was 24.0% in one Western study (121). Among those, LNM risk was not detailed according to mucosal or submucosal invasion status (90–93,95,96,99,100,119,120,237,283,299,314). From other studies, LNM rate for mucosal and submucosal SRC-GC reached 0% to 9.9% (116–118,124,130,238,302,303,306–308,311,312,315) and 7.1% to 28.8% (116–118,124,130,238,302,303,306,308,311–313,315) respectively. Consequently, taking into account depth of invasion, only mucosal SRC-EGC may be considered for ER.

Table 7: Series reporting risk of LNM according to depth on invasion in SRC EGC. LNM: lymph node metastasis; ER: Endoscopic resection; SRC-EGC: early signet ring cells gastric cancer;

Authors	Country	n total	SRC EGC LNM (%)		
			mucosal (n)	submucosal (n)	both
Eastern studies					
Maehara 1992 (99)	Japan	28	-	-	10.7%
Kim 1994 (93)	South Korea	185	-	-	7.6%
Otsuji 1998 (100)	Japan	28	-	-	5.3%
Hyung 2002 (91)	South Korea	263	-	-	5.7%
Abe 2004 (299)	Japan	104	-	-	11.5%
Kim 2004 (119)	South Korea	94	-	-	2.1%
Kunisaki 2004 (95)	Japan	120	-	-	9.2%
Ye 2008 (315)	South Korea	316	1.8% (219)	15.5% (97)	6.0%
Ha 2008 (116)	South Korea	388	1.6% (258)	25.4% (130)	9.5%
Kunisaki 2009 (314)	Japan	378	-	-	10.3%
Park 2009 (306)	South Korea	215	2.9% (138)	16.9% (77)	7.9%
Lee 2010 (130)	South Korea	448	5.9% (304)	20.8% (144)	10.7%
Tong 2011 (308)	China	102	3.5% (57)	28.8% (45)	14.7%
Chiu 2011 (90)	Taïwan	149	-	-	10.7%
Jiang 2011 (92)	China	54	-	-	16.6%
Kim 2011 (238)	South Korea	419	2.9% (313)	14.2% (106)	5.9%
Huh 2013 (237)	South Korea	540	- (371)	- (169)	5.9%
Kwon 2014 (96)	South Korea	51	-	-	9.8%
Kim 2014 (118)	South Korea	345	6.3% (222)	13.8% (123)	9.0%
Wang 2014 (311)	China	136	3.8% (79)	19.3% (57)	10.3%
Lee 2015 (124)	South Korea	114	1.3% (76)	7.9% (38)	3.5%
Asakawa 2015 (283)	Japan	315	-	-	6.7%
Wang 2015 (120)	China	115	-	-	8.5%
Guo 2015 (302)	China	198	9.9% (141)	21.1% (57)	13.1%
Imamura 2016 (117)	Japan	152	0% (110)	7.1% (42)	2.0%
Pyo 2016 (307)	South Korea	1544	3.8% (1544)	-	-
Kim 2017 (313)	South Korea	179	-	7.8% (179)	-
Lee 2017 (303)	South Korea	652	2.5% (499)	14% (153)	5.2%
Kang 2017 (312)	South Korea	91	1.5% (66)	16% (25)	5.5%
Western studies					
Gronnier 2013 (121)	France	104	-	-	24.0%

Macroscopic criterion: size criteria and ulcer presentation

Tumor size (58,124,238,288,296,297,299,303,305,310) and ulcer presentation (296,305) have been also showed as independent risk factors of LNM. The size of lesion has to be specifically taken into account for ESD in SRC-EGC. Several publications reported difficulties in accurate estimation of the size and margin of the lesions. Kang et al. found a significant higher size discrepancy between pretreatment endoscopy and resected specimen with ESD in UD-EGC (including 30 SRCC) than differentiated EGC (p=0.002). The complete resection rate was significantly lower for UND-EGC than differentiated-EGC (55% vs 84.1%; p<0.001) (316). Likewise, a study dedicated to endoscopic treatment in SRC-EGC reported underestimations of 30.2% in lesional sizes. In that study, EGC larger than 2 cm were considered as risk factor for underestimation (317).

Expanded criteria

Criteria to decide whether ER may be curative include depth of invasion, size, lympho-vascular invasion and ulcer presentation.

The Japanese gastric cancer association (JGCA) guidelines 2010 separate the standard treatment (absolute indications) to investigational treatment (expanded indications) (318). EMR/ESD is indicated as a standard treatment for differentiated-type adenocarcinoma without ulcerative findings (UL(-)), limited to the mucosa and ≤ 2 cm. ESD should be offered (expanded criteria) with caution for tumors clinically diagnosed as T1a and:

- of differentiated-type, UL(-), but > 2 cm in diameter
- of differentiated-type, UL(+), and ≤ 3 cm in diameter
- of undifferentiated-type,UL(-),and ≤ 2 cm indiameter.

Hirasawa et al. provided robust evidence that there was no risk of LNM in patients with UND-EGC fulfilling the expanded criteria of the JGCA (0/205) (319).

A large phase II study was conducted in Japan to prove long-term safety and effectiveness of ESD in UND-EGC, results are still awaited (UMIN Clinical Trials Registry as UMIN000004995) (320).

Taken together, Shim et Lee proposed, a treatment algorithm for UND-EGC (figure 4) according to those 4 criterion, consistent with the conditions of curative resection according to the JGCA treatment guidelines (321).

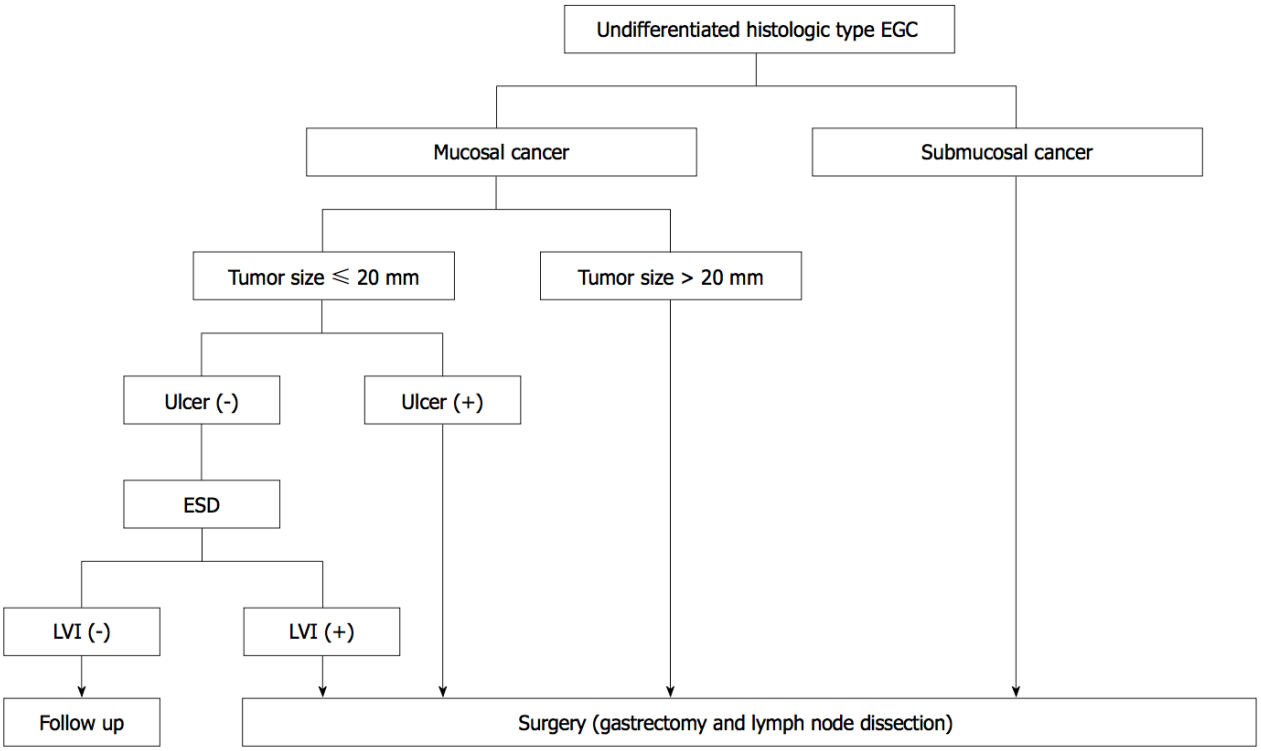

Figure 4: Treatment algorithm for undifferentiated type early gastric cancer according to depth of invasion, tumor size, ulceration, and lymphovascular invasion. EGC: Early gastric cancer; ESD: Endoscopic submucosal dissection; LVI: Lymphovascular invasion. (Scheme from Shim et al. WJG 2014 (321))

Among UND-EGC, poorly differentiated-EGC have been shown to be associated in multivariate analysis to presence of ulcer, submucosal invasion, and LVI, compared with SRC EGC (238). Despite the absence of clear guidance due to the lack of randomized controlled trial (RCT), ESD is consequently proposed for the treatment of SRC-EGC fulfilling accurate criteria by an increasing number of institutions (90,91,116,124,125,238,303,306,308,309,311,312,314–316,322–325) with excellent survival results (322,325,326). Some authors used more restricted criterion regarding the size and reported that SRC-EGC with mucosal invasion, size <15 mm, and no-LVI had no LNM (n=0/47) (238).

In conclusion, despite an increasing number of publications, SRC-EGC still have not been approved generally as a standard endoscopic treatment in Asia (318) but ESD may constitute a sufficient option in non-ulcerated lesions ≤ 2 cm in diameter, limited to mucosa and without LVI. In Western countries, the European Organisation for Research and Treatment of Cancer St. Gallen International Expert Consensus defined the indications for

ER in EGC, largely following JGCA guidelines, except for diffuse EGC for which surgery is considered mandatory (327). The specific case of SRC-EGC is not addressed as well as in American recommendations (277).

Surgery

Gastrectomy

Current guidelines

JGCA recommends a proximal margin of at least 3 cm for AGC with an expansive growth pattern and 5 cm for those with an infiltrative growth pattern. When these rules cannot be observed, it is advisable to examine the proximal resection margin by frozen section. For EGC, a gross resection margin of 2 cm should be obtained (328).

Current Western guidelines support total (TG) or subtotal gastrectomy (SG) for AGC depending of the location of the tumor (276,329). Quality of life has been shown to be significantly better after SG than after TG (330). Two RCT have investigated whether SG is sufficient compared with TG for distal GC and found no significant difference in mortality or survival (331,332). In the French trial (332), LP was an exclusion criteria and only tumor differentiation was analyzed. In the Italian trial, 40% of the patients had a diffuse type tumor according to Laurén's classification but no subgroup analysis was performed.

In the ESMO guidelines, SG may be carried out if a macroscopic proximal margin of 5 cm is achieved (276). For diffuse GC, a margin of 8 cm is advocated, otherwise, a TG is indicated (276).

In the National Comprehensive Cancer Network (NCCN) guidelines, SG may be carried out if a macroscopic proximal margin of 4 cm is achieved (329).

The Italian Research Group for Gastric Cancer (GIRCG) recommends a proximal margin of at least 3 cm for T2 or deeper tumors with an expansive growth pattern, and 5 cm for those with infiltrative growth pattern and diffuse Laurén's histotype. When these rules cannot be respected, they advise to examine the proximal resection margin by frozen section (333).

In the French recommendations (http://www.tncd.org) (334) a proximal margin of 5-6 cm and a distal margin of 2-3 cm are advocated. SRC-GC are not indivualized. For LP it is specified that TG should be performed with a frozen section analysis of esophageal and duodenal sections.

Degree of extend of gastrectomy

SRC-GC and diffuse AGC have been shown to be associated with higher risk of positive resection margins due to specific infitrative characteristics (15,16,129,335,336).

Distally, SRCC and other PCC at antroplyoric region have a propensity to invade duodenum via submucosal and subserosal routes and lymphatic spaces. A distal margin frozen section is consequently requested at the time of surgical resection (37).

Proximally, whether a systematic TG for SRC-GC should be proposed is questionable, due to the (i) infiltrating nature and (ii) risk of pitfall in evaluation of proximal frozen after SG (ie size of margin and risk of false negative results). A recent study carried out on 46 patients with SRC-GC patients, who underwent TG (n=26) or SG (n=20) did not find any difference in term of OS rate (respectively 42.2% vs 58.2%; p=0.417). The authors concluded SG can be performed safely for patients with SRC-GC and is equal to TG with respect to prognosis and complication rates (337). Marrelli et al. confirmed in a multicenter longitudinal study the validity of SG in the treatment of distal diffuse-type neoplasms when an adequate margin of distance from the tumor is obtained and microscopic examination does not show infiltration of the resection margins (218).

Spicer et al. studied retrospectively the accuracy and utility of intraoperative microscopic margin analysis of 81 patients with gastro-esophageal adenocarcinoma (GEA) who underwent surgery The diagnostic accuracy of frozen section at the proximal margin was 93% with sensitivity=67%, specificity=100%, positive predictive value=100%, and negative predictive value=91%. The majority of false negatives (83% (5/6)) occurred in patients with SRC pathology due to difficulties to identify rare SRC in an abundant stroma (338). Thus, the negative results on frozen section require greater caution for both the surgeon and the pathologist when SRC are present.

To conclude in case of LP, a total gastrectomy with frozen section of both distal and proximal margins should be performed. For distal SRC-AGC and diffuse type, a subtotal gastrectomy may be proposed with at least 5-8 cm of proximal margin with otherwise either a TG or a frozen section of the margin. Distal margin should be systematically analyzed on a frozen section due to the specific risk of duodenal invasion.

Lymphadenectomy

Current recommendations in Europe and USA are D2 modifed lymphadenectomy (D2 without splenopancreactectomie) for AGC (276,329,339,340). However, lymph node dissection for T1 tumors not accessible to ER may be confined to perigastric lymph nodes and include local N2 nodes (D1+, with variation in nodal groups dissected according to the site of cancer) (276). The JGCA recommends D2 lymphadenectomy for potentially curable T2-T4 tumors as well as for cT1N+ tumors. The final results of a randomized trial (JCOG 0110) do no support systematic splenectomy unless the primary T2-T4 tumor either directly invades the spleen or is located in the greater curvature of the upper stomach (341).

Due to a higher risk of LNM in SRCC when compared to non SRCC (13,15,105,109,214) whether the extend of lymphadenecomy should be adapted is questionable. This question is not addressed in any randomized trial published on the topic.The GIRCG Guidelines recommend a larger lymphadenectomy (D2 plus) (posterior stations (8p, 12p/b, 13), along the superior mesenteric vein (14v) and the additional removal of paraaortic nodes (16a2, 16b1)) for Laurén's diffuse histotype located in the distal two-thirds of the stomach because of a higher risk of LNM (333).

Peri-operative treatments

Neoadjuvant/ perioperative chemotherapy setting

After R0 surgery, the two main risk factors of recurrence are LNM and depth of invasion (243). Recurrence occurs in 37 to 55% of cases with locoregional recurrence in up to 32.5% of cases and peritoneal recurrence in up to 45.9% of cases (342,343). Consequently strategies of perioperative treatments (pre- and/or post-operative) have been tested in several phase III trials in order to increase the OS rate and DFS compared with surgery alone. However SRC-GC are hardly ever identified in these studies and wether perioperative treatment should be tailored is questionable.

Is SRCC chemoresistant?

The advantage of perioperative chemotherapy (CT) over surgery alone in GC has been demonstrated in two phase III randomised trials (MAGIC and FNCLCC/FFCD) (344,345). Epirubicin-Cisplatin-5-FU scheme (ECF) regimen (344) became a standard in Europe, with an option for the 5-FU- cisplatin scheme (CF) (345). Perioperative CT

allowed an increase in R0 resection resection, tumor and lymph node downstaging and provided a significant improvement of OS in patients with GC. However, no trials have been dedicated to the study of SRCC, and no stratification according to the SRC subtype has been performed. However in the MAGIC trial, a post hoc analysis published in 2016 showed that neither Lauren's histologic subtype was statistically significantly more likely to demonstrate a good pathologic response to chemotherapy. However only 18% of patients had diffuse type cancer and presence of SRC were not evaluated (346).

Several studies, mainly retrospectives, have suggested that SRC-GC were less chemosensitive than non-SRC-GC (14,22,23,29,108,109,187). Similar findings were reported for Laurén's diffuse type GC (29,266,347–350). In a phase II study, Rougier et al. studied the impact of neoadjuvant CT with 5-FU and cisplatin in 30 patients with locally AGC; the tumor response rate was 56% in the overall population compared to only 16% in patients with LP. The lower response rate was associated with significantly worse survival (p=0.002) (351)(187). Using the same CT regimen, Takiuchi et al. found a lower response rate in diffuse compared with intestinal GC type (22.2% vs. 83.3%) (350).

In 2011, we used a large multicenter retrospective comparative cohort (ADCI001) to investigate the impact of perioperative CT on survival in patients with SRC-GC. Among 3010 patients registered retrospectively, 1050 had a SRC-GC (45.4%). After exclusion of 126 metastatic patients at diagnosis, 924 patients were analysed in an intention to treat process comparing primary surgery (n=753, 81.5%) (S group) vs perioperative chemotherapy (CT group) (n=171,18.5%). The CT were essentially CF (39.2%) or ECF regimens (42.3%) and were administered for 2 to 4 cycles perioperatively. The two groups of patients were strictly comparable in terms of demographic characteristics (age, sex, American Society of Anesthesiologists score, malnutrition) and tumor characteristic (location, clinical pre-treatment TNM). No tumor downstagging was observed in the CT group with consequently more extended surgeries (more total gastrectomies and more extended surgery to esophagus or neighboring organs). At pathological examination no significant downstaging (stage pT and pN) and no benefit in terms of R0 resection was observed in the CT group. An adjuvant treatment was carried out more frequently in the CT group (64.8% vs 33.5%, p<0.001). Recurrence rates were similar between groups and occuried earlier in the CT group (7.9 vs. 12.2 months, p=0.015). The median survival was significantly better in the surgery first arm than in the CT first arm (12.7 vs. 8.6 months) (p<0.001). The OS rate for 2 years was 27.1% in the S group as opposed to 12.3% in the CT group. In multivariate analysis, administration of a preoperative CT constituted an independent factor of poor prognosis in multivariate analysis (HR=1.4, p=0.042) (14). This

results suggested a possibly harmful role of CT at the preoperative stage with the following hypothesis: (i) innate chemoresistance of SRCC, (ii) disease progression during neoadjuvant CT and (iii) toxicity causing a relative immunodepression of the host facilitating progression of the disease (352). Despite several biases, this study also highlighted the urgent need for (i) randomized trials dedicated to SRCC (or stratified on the SRC subtype) to test different therapeutic strategies and/or chemotherapeutic regimens. We consequently designed the PRODIGE-19-FFCD1103-ADCI002 trial, which is a prospective multicentre, controlled randomised phase II/III trial comparing current standard of care of perioperative CT (2x3 cycles of ECF) with a strategy of primary surgery followed by adjuvant CT (6 cycles of ECF) in patients with a stage IB-III SRC-GC. The principal objective of the phase II study (84 patients) is to determine if the experimental arm (primary surgery followed by adjuvant CT) has sufficient interest in terms of percentage of living patients at 24 months to be evaluated in a phase III trial (353). Results are awaited for the end of 2018.

Voron et al confirmed that pre- and postoperative CT did not significantly impact on survival following resection of SRC-GC (n=899), whereas it was significantly beneficial in non-SRC-GC (n=900) (109). Concordantely, Lorenzen et al. concluded that histopathologic non-response to preoperative CT tended to be higher in diffuse type vs. intestinal type (92.9% vs. 76.7%, p=0.075)) (354). Another large retrospective study (n=723 GEJ and GC including 235 SRCC), in a perioperative setting, suggested that SRCC had a lower clinical response rate (21.1 vs. 33.7%, p=0.001) and histopathological response rate (16.3 vs. 28.9%, p<0.001) to neoadjuvant CT (mostly 5FU + platinum) than non-SRCC (23). However, the authors noted that among the small category of SRCC with a clinical or a pathological response, the outcome was favorable and consequently concluded that perioperative CT should not be abandonned in SRCC. In this study, addition of taxanes influenced positively prognosis, but not in R0-resected patients or SRCC (23). However, several studies recently published in the litterature suggest a potential role of taxane-based regimen in SRCC.

Taxane based regimen: a new hope?

A new craze for taxane-based-CT in GEA recently appeared with likely effect on SRC histologic subtype. However, results remain controversial (23,347,355–357). A retrospective multicenter, hypothesis-generating study, suggested an OS benefit from the docextaxel-cisplatin-5-FU regimen (DCF) (n=60) in resectable GEA compared to standard

CT (n=399) with a 3-year OS rate of 73.6% (95% CI 57.4-84.5) for the DCF group, while it was 49.0% (95% CI 42.5-55.2) for the S group. Only 6 patients with SRCC received the DCF regimens (357). A retrospective series of localized SRC-GEA (n=19) series evaluated the impact of taxane-based preoperative CT. Seven-teen patients underwent surgery. Complete resection was achieved in 80 %, and median OS was 40.8 months (95 % CI, 20.2-not reached). Even though 10 patients had a response (including one pathological complete response (pCR)) or non progression, seven patients had an upstaging of their tumors at surgery. Thus, the potential benefits of taxane-based CT seemed to be limited to a reduced number of patients (356).

In Germany, the FLOT regimen (5-FU, leucovorin, oxaliplatin and docetaxel) has increasingly developed and been evaluated with subgroup analysis according to histological type. A prospective study and a phase II study (NeoFLOT) reported high pathological reponse rates using FLOT regimen with pCR rates of 17.4% and 20%, respectively (358,359). Interestingly the authors analyzed histological response according to Laurén's classification. In the first study the pCR rate was higher in intestinal than in diffuse/mixed type GA (30.8% vs. 0%, $p<0.05$) (358). In the NeoFLOT study, when considering near complete responders (<10% residual tumor), 85% had intestinal, 10% had diffuse and 5% had mixed type tumors (359).

FLOT4-AIO (NCT01216644) is a randomised, open-label, multicenter, phase 2/3 German study comparing for gastric and GEJ adenocarcinoma of stage ≥cT2 and/or cN+ 2 perioerative regimens: 6 cycles of ECF/ECX vs. 8 cycles of FLOT. The interim analysis showed a significant higher proportion of patients achieving pCR in the FLOT group than in the ECF/ECX group (16% vs 6%, $p=0.02$). Overall, pCR rate was higher in intestinal than in diffuse type tumors (16.1% vs. 2.7%; $p=0.004$)). The rate of pCR for intestinal tumor type was higher with the FLOT than with ECF/ECX regimen (23% vs. 10% $p=0.07$). However, pCR rate was similar between FLOT and ECF/ECX diffuse tumor type (3% vs 3%, $p=1$) (347). Favorable pathological regression with FLOT was consistent with two additional findings: more patients achieved surgical resection with FLOT compared with ECF/ECX, and, in patients undergoing resection, there was a greater proportion of postoperative stage ypT0, ypT1, or ypT2 tumors with FLOT than with ECF/ECX.

Updated analysis with long-term survival data has been presented at ESMO 2017 congress (355). Compared to ECF, FLOT was associated with less progressive disease cases during/after preoperative therapy (1% vs. 5%; $p<0.001$), more R0-resections (84% vs. 77%; $p=0.011$), higher number of pT0/pT1 tumors (25% vs. 15%; $p=0.001$), longer progression-free (30 vs. 18 months; HR 0.75; $p=0.001$) and OS (50 vs. 35 months;

HR=0.77; p=0.012). In multivariate analyses, parameters associated with favorable survival were FLOT therapy (HR 0.75, p=0.006); stomach as the primary (HR 0.74; p=0.005), and nodal negativity (HR 0.72, p=0.022). Age and Laurén's type of histology had no impact on survival. Interestingly, the authors showed subgroup analysis. Patients benefited from FLOT even if they were old (≥70), had small tumors, a nodal negative status, or a SRC component. No benefit was described in the diffuse type. Results of the publication are awaited since the histological defintion of the authors to define SRC was not detailed in the presentation.

In conclusion, whereas SRCC is thought to be less chemosensitive than non-SRCC, recent reports suggest it could have a specific sensitivity profile and be more sensitive to taxane-based CT (355). Because of the benefit of CT in a perioperative setting is controversial, a prospective RCT is under way to test this hypothesis (353) (PRODIGE 19).

Georgraphical influence

In the East, whereas adjuvant CT is the preferred therapeutic strategy in GC, 2 trials evaluating preoperative CT dedicated to LP have been identified (360,361).

A phase II trial (JCOG 002) evaluated the results of neoadjuvant CT with S1 in patients with LP (n=55). A staging laparoscopy with negative peritoneal cytology was mandatory (361). Among 43 evaluable patients, the tumor response rate was 32.6% with good tolerance. The curative resection rate was 80.8%, with acceptable morbidity and no mortality. The survival curve at 2 years of follow up showed a better survival rate than that of the historical controls, but did not reach the expected survival rate and consequently no phase III was performed.

A second JCOG phase II trial evaluated the results of neoadjuvant S-1 and cisplatin combination in patients with LP (360). Tumor response was 76% above the predetermined objective. Consequently, a Japanese multicenter randomized phase III trial (JCOG 0501) was designed comparing primary surgery versus neoadjuvant S-1 and Cisplatin followed by surgery in 300 patients with Bormmann IV or large type III (>8 cm) GC. This RCT has been conducted from November 2005 to April 2015, and results are awaited (NCT00252161).

Adjuvant CT

In the meta analysis of randomized trials testing the interest of adjuvant CT in GC published in 2010, individual data, 17 trials were analyzed (3838 patients) (362). Administration of adjuvant CT was associated with an improvement in OS and DFS (HR 0.82, p<0.001) with an absolute advantage in terms of survival after 5 years of 5.8% and 7.4% at 10 years. Regimens based on 5-FU were the most effective. There was no significant heterogeneity between the studies from the continents of Asia, America and Europe. No analysis according to histological type was done.

Adjuvant CT is considered as the referral treatment only in Asia, at present based on two major RCT: the ACTS-GC (Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer) trial and the CLASSIC sudy (363,364).

In the Japanese study ACTS-GC, 1059 patients, operated on for curative purposes with D2 removal of a stage II or III tumor were randomised between monochemotherapy with S1 (fourth generation of oral fluoropyrimidine) and monitoring. After three years monitoring, OS rate and DFS rate significantly favoured the S1 arm (80.1% vs 70.1%, p=0.0015 and 72.2% vs 59.6%, p=0.0001 respectively). There was no subgroup analysis based on diffuse or SRC-GC type. However, S-1 setting had a significant favourable HR for death in the undifferentiated group compared to surgery alone contrary to in the differentiated group where the effect was not significant (363). Sasako et al reported the 5-year results of the ACTS-GC, the OS rate was 71.7% in the S-1 group and 61.1% in the surgery-only group (HR: 0.669, 95% CI 0.540 to 0.828) and the DFS rate was 65.4% in the S-1 group and 53.1% in the surgery-only group (HR, 0.653 95% CI 0.537 to 0.793). These survival differences were highly statistically significant. After 5 years, the results were maintained an intrerestingly the subgroup analysis of both differentiated and undifferentiated tumor showed a significant benefit with S1 (365).

The CLASSIC, phase 3 open-label RCT undertaken in 37 centres in South Korea, China, and Taiwan evaluated adjuvant capecitabine and oxaliplatin (OX) for GC versus observation alone after D2 gastrectomy. A total of 1035 patients were randomised (520 to receive CT after surgery, 515 surgery only). The primary outcome, 3-year DFS was 74% (95% CI 69–79) in the CT and surgery group and 59% (95% CI 53–64) in the surgery only group (HR 0.56, p<0·0001). The estimated 5-year DFS was 68% (95% CI 63–73) in the adjuvant CT group versus 53% (95% CI 47–58) in the observation group (364). No analyze according to histological subtype was yet published.

Chen et al. evaluated the benefit of adjuvant CT between GA, absolute SRC-GC and mixed SRC-GC. OS and DFS were better in the CT arm (either oxaliplatin or docetaxel based) than surgery alone ($p<0.001$) without any difference between the two CT regimen groups. In the absolute SRC-GC group, OS and DFS were similar between CT arms and surgery only group. In contrast to absolute SRC-GC, adjuvant CT benefited from the mixed SRC GC group (both oxaliplatin and docetaxel-based CT) in term of OS and DFS. Interestingly, OS and DFS were significantly longer with the docetaxel-based regimen than oxaliplatin-based one (29). This study supports the facts that SRC GC could behave differently according to the percentage of SRC and underlines the potential benefit of taxane-based CT in SRC GC.

Radio-chemotherapy therapy strategies

A meta-analysis published in 2009 attempted to evaluate the impact of RT (preoperative, postoperative or peroperative) on survival at 3 and 5 years in resectable GC or GEJ compared with a strategy of surgery alone or combined with CT (366). Nine studies including a total of 2025 patients were selected (242,367–374) . The result of this meta-analysis showed a significant benefit of RT in terms of 5-year survival (RR 1,26, p=0.004).

Post operative chemo-radiotherapy (CRT)

after primary surgery

Because of a higher rate of locoregional than rate of metastatic relapse of GC, surgery alone therefore remains insufficient in terms of loco-regional control and the addition of local treatment with radiotherapy (RT) seems attractive in theory and has long been considered a s a standard in USA (131,349,375).

The Intergroup 0116 RCT compared monitoring with CRT (5-FU+leucovorin + 45 Gy) in 582 patients with GA (80%) or GEJ adenocarcinoma (20%) at stage IB to IVM0 according to the 1988 staging criteria of the American Joint Committee on Cancer, operated on for curative purposes (R0 resection) (Macdonald et al., 2001). The absolute benefit of OS was 11% after 2 years. The median duration of survival was 35 months in the adjuvant treatment arm vs. 26 months in the monitoring arm (p=0.005). The results of this trial were broadly critical because of the poor quality of the surgery particularly in terms of removal of lymph nodes (54% of patients underwent removal D0), which may have artificially favoured the CRT arm. An update of the results with median monitoring of over 10 years showed that this difference was maintained in terms of OS (HR 1.32,

p=0.004) and survival without recurrence (HR 1.51, p<0.001). The 10-year follow-up of this study showed that in contrast to intestinal-type (n=263), the diffuse-type (n=169) do not benefit from postoperative CRT in subgroup analysis (349).

The randomised CALGB 80101 study included 546 patients who had undergone a curative resection of stage IB through IV (M0) gastric or GEJ adenocarcinoma. Postoperative CRT using a multiagent regimen of ECF before and after RT did not improve survival compared with standard 5-FU-leucovorin before and after RT. No survival benefit according to the grade of differentiation were noted in subgroup analysis (376).

Finally the results of the randomised Korean ARTIST study comparing the administration after surgery with removal D2 of CT with capecitabin + cisplatin whether (n=230) or not (n=228) combined with RT found similar DFS and OS but subgroup analyses also showed that CRT significantly improved DFS in patients with node-positive disease and with intestinal-type GC (377). A further trial including only patients with node positive disease is in course (ARTIST 2 trial, NCT01761461) with 3 arms testing S-1, S-1-oxaliplatin with or without RT in D2 resected GC.

After neoadjuvant chemotherapy

The European Dutch CRITICS study, aimed to compare after neoadjuvant CT (ECX) and surgery with removal of lymph nodes of at least D1, the administration of adjuvant CT using the same scheme with CRT (378,379). The results of this trial recently published showed that that patients with resectable GC treated with preoperative CT and adequate surgery do not benefit more from postoperative CRT than postoperative CT. Subgoup analysis according to histologic subtypes showed no difference between intestinal (n=253) and diffuse (n=233) type tumors.

Overall, at present all RCT evaluating the potentail benefit of adjuvant CRT failed to show a favorable outcome in the SRC-GC ou diffuse type GC. An analysis of the SEER database using a propensity score however showed favourable outcome of adjuvant RT in patients with diffuse-type GC (median survival time: 30 months with adjuvant RT vs. 18 months without adjuvant RT, p<0.001, HR: 0.75, p<0.001). One of important biais was the absence of knowledge regarding the use of CT (380).

Neoadjuvant CRT

Phase III trials which evaluating RT or preoperative CRT in GC, excluding the GEJ, are few and small (370–372). Several phase II trials showed encouraging results in terms of tumor response and survival but this type of strategy has up to now been limited by the toxicity caused (381–385). At least two trials are in course: TOPGEAR (386) and CRITICS-II (NCT02931890) with hopefully planned subgroup analyses according to histological type.

A study analysing 107 localized GC (n=45 non-SRC-GC and n=62 SRC-GC) treated with preoperative CRT showed presence of SRC was associated with a lower rate of pCR (11% vs 36%, p=0.004) and the association remained significant even with low percentage of SRC (1–10%; p=0.014). Higher the fraction of SRC, the lower was the probability of pCR (p=0.03). Poorly differentiated and SRCC led to shorter OS (p=0.046 and p=0.038, respectively) (22).

Intraperitoneal chemotherapy (IPC) combined with surgery

Preventive

The failure rate of surgical curative treatment for patients with GC is mainly due to peritoneal recurrence, especially in SRC-GC and LP cases (15,207,240,241,243–247).

Two recent meta-analysis of RCT mostly Asian showed a benefit of administrating prophylactic IPC but there was not subgroup analysis taking into account histological type including SRC-GC (387,388). Further clarification of the effects and safety of adjuvant IPC is needed especially in Western population since intraoperative CT might be of greater benefit because of more advanced disease. The ongoing GASTRICHIP study is a phase III randomised European multicentre trial (NCT01882933) evaluating the role of HIPEC (hyperthermic intraperitoneal chemotherapy) with oxaliplatin in patients with GC with either serosal infiltration and/or LNM and/or positive peritoneal cytology treated by a curative gastrectomy. A stratification of SRC-GC vs. non-SRC-GC has been anticipated and will alow an accurate analysis of the results in this subgroup of patients (389).

Curative

A panel of international experts strongly recommend that cytoreductive surgery (CRS) plus HIPEC is the current standard treatment for AGC (390,391). Nevertheless, controversy over this treatment modality remains, and more high quality clinical studies are required to clarify the value and the usefulness of this strategy, which could be of particular interest for SRC-GC. At present, no study compared CRS+HIPEC versus CT alone. A multicenter, open label, phase I-II study (PERISCOPE) is ongoing in the Netherlands and will determine the safety, tolerability, and feasibility of gastrectomy combined with cytoreduction and HIPEC using oxaliplatin in combination with docetaxel after systemic CT as primary treatment option for GC patients with tumor positive peritoneal cytology and/or limited PC (392). PERISCOPE 2 will randomize CT alone versus cytoreduction +HIPEC with chemotherapy (using the best arm of PERISCOPE 1).

Before 2018

A randomized phase III study demonstrated the benefit of HIPEC (cisplatin and mitomycin C) associated with CRS. Median survival was 11 months in the CRS + HIPEC group as compared to 6.5 months in the group receiving CRS alone (p=0.046). CRS + HIPEC was an independent predictors for better survival. No subgroup analysis in term of histologic type could be done (393). The GASTRIPEC trial (NCT02158988) is currently ongoing comparing CRS + HIPEC with CRS alone in patients with GC and synchronous peritoneal. This trial is anticipated to be completed by September 2020.

A large multicentric retrospective serie of curative CRS and HIPEC included 159 patients with PC from GC showed an interesting OS with a 5-year survival rate until 23%. No significant prognostic impact of tumor differentiation was shown. No subgroups analysis according to histological type was performed (394).

A single small retrospective series of patients with PC from SRC-GC (n=18) has been published (280). Complete cytoreduction could only be achieved in 72% of patients. The median survival for patients after CRS and HIPEC was 8.9 months. SRC-GC presented more advanced PC thant non SRC-GC. The authors concluded that CRS and HIPEC should be restricted to highly selective patients in order to avoid exploratory laparotomy (280).

How to select patients

From those published, patients who may benefit from CRS and HIPEC are those with Sugarbaker's Peritoneal Cancer Index (PCI) less than 12, following response to neoadjuvant CT, with no diffuse small bowel involvement demonstrated by CT-scan and laparoscopy, and with a high probability of complete macroscopic cytoreduction (393,394). Recently, Chia et al. evaluated also in a French multicentre retrospective study the interest of CRS + HIPEC in patients with PC from GC. Among 89 patients, 59 had a completeness of cytoreduction score with a median PCI=6. The 5-year OS rate was 18 %, with nine patients still disease-free at 5 years. Patients without SRC-GC (n=29) showed a better OS than SRC-GC (21.8 vs.13.2 months, p=0.0214). The authors suggested that for patient with PCI < 7 and an achievable complete cytoreduction, the presence of SRC should not prevent from CRS and HIPEC (395).

In 2018

The CYTO-CHIP study is a French multicentric retrospective study collecting data from 277 consecutive patients treated for GC with PC from 1989 to 2014 in the FREGAT and BIGRENAPE databases. A total of 180 patients who underwent CRS and HIPEC were compared to 97 treated by CRS alone. Only patients treated by complete CRS were included (CC-0 or CC-1). After propensity weighting, groups were similar except for the PCI that remained higher in the HIPEC group (median: 6 vs 2, p=0.003). However, there was no difference in the completeness of CRS (CC-0: 76.7% vs 83.5 %, p=0.904). Compared to CRS alone, HIPEC was associated with increased OS and potential disease eradication for GC with PC, without additional morbidity. Subgroup analysis in patients with SRC-GC confirmed the superiority of HIPEC and CRS (396).

Pressurized intraperitoneal aerosol chemotherapy (PIPAC)

Pressurized intraperitoneal aerosol chemotherapy (PIPAC) is a promising novel technique of intraperitoneal CT. Retrospective analyses of PIPAC were applied in 24 consecutive patients with PC from GC (18 patients had SRC-GC). The objective tumor response was observed in 50% of cases (397). The results of the German study PIPAC-GA01, NCT01854255) are awaited. This new procedure seems to be attractive in PC from GC in a palliative setting hoping to lead patients to curative resection.

Palliative therapeutics

Surgery

SRC-GC are more often associated with non curative surgery (15,398) and in case of palliative resection the prognostic is poorer for SRC histology (HR 1.6, p=0.02) (398).

An Asian RCT (REGATTA) evaluated the interest of palliative gastrectomy and CT vs. exclusive CT (oral S-1 and Cisplatin in both arms) in patients with a GC with one site metastasis. No significant benefit in terms of survival was found but there was a higher rate of grade 3 or 4 CT-associated adverse events in the experimental group (399). The subgroup analysis based on Laurén's classification did not find any benefit in both arms.

In a retrospective multicentric study, only a few selected patients with SRC-GC benefited from palliative resection in term of OS when compared to exclusive CT: ASA I-II patients with incomplete resection locally or with one site solid organ metastasis did whereas patients with localized or distant PC did not (400).

Chemotherapy

Several studies demonstrated that SRCC had different infiltrative and metastatic mechanisms than non-SRCC. It lacked free ribosomes but were rich in lysosomes and mucus impeding anticancer drug to get to the cell (45,237). In a metastatic setting there are few data concerning chemosensitivity in specific subsets of SRCC in prospective trials.

5-FU and platin based chemotherapy

Dedicated studies

Rougier et al reported among 87 patients with metastatic or recurrent tumor (n=57) or with locally AGC (n=30) a significantly poorer response rate of CT using infusional 5-FU and cisplatinum for LP or SRC histology (p=0.003 and p=0.16, respectively) (187).

A phase II Asiatic study evaluated the advantage of CT with 5-FU, cisplatin and methotrexate in 47 patients with diffuse GC in palliative situation (401). A tumor response rate of 38.3% was observed with patients with intolerance to food regaining their diet in 71% of cases. This scheme was never compared with the standard schemes, which have currently been validated in a randomized study.

A retrospective study compared CT with S1 (n=19) vs. non-S1 CT (mainly 5-FU, cisplatin, methotrexate and mitomycin C) (n=34) in patients affected by unresectable LP.

The rate of tumor response and OS were significantly better in the S1 group (57.9% vs 27.9%, p<0.01 and 402 days vs 213 days p<0.001, respectively) with in addition less hematological toxicity in the S1 group (402).

Subgroup analysis studies

A phase III study (SPIRITS), showed the superiority of a combination of S1 with cisplatin compared with S1 alone in patients with a locally AGC with an advantage in terms of OS and survival without progression (p=0.004 and p<0.001, respectively) at the price of greater toxicity. Subgroup analysis did not show any difference between intestinal and diffuse histologic types (403).

The FLAGS trial recently published, included 1053 non Asiatic patients with non resectable GC or GEJ adenocarcinoma (404). The aim of this study was to demonstrate the superiority of a scheme of S1-cisplatin versus a scheme of 5-FU plus infusional cisplatin. The OS was 8.6 months in the S1 arm versus 7.9 months in the 5-FU arm with no significant difference between the two groups (p=0.20). Once again, toxicit was significantly less in the S1 arm. An analysis of the sub-group was carried out in SRC-GC. There was better OS in the S1 group compared with the 5FU group (9 vs. 7.1 months, p=0.004) emphasising the potential of this form of continuous oral administration or the molecule itself in cases of SRC-GC (404).

In total, in SRC-GC the oral form of 5-FU and more specifically S1 seems to have a very particular advantage without us knowing exactly whether it is the oral form, and therefore the continuous administration, which ensures its better efficacy. As a reminder, S1 is an active combination of tegafur (prodrug of 5-FU), gimeracil (extending the lifetime of 5-FU), and oteracil (improving the digestive tolerance of the medicinal product. S-1 which was shown to be able to cross the peritoneal barrier (405) with a tumor response in almost half the cases in two retrospective Asiatic studies (406,407). However S-1 does not have marketing authorization in Europe in metastatic GC. There is a phase III trial ongoing which is evaluating the safety and efficacy of S-1 and cisplatin compared to 5-FU and cisplatin in treatment of patients with metastatic diffuse gastric and GEJ adenocarcinoma previously untreated with CT (408).

Taxanes-based chemotherapy

A study of the AGEO evaluated the place of docetaxel added to 5-FU, leucovorin and oxaliplatin (TEFOX) as first-line treatment in 65 patients with metastatic ou locally

advanced non-resectable gastric ou GEJ SRCC including 17 LP. This regimen gave an interesting response rate of 66% with an OS of 14,3 months. Interestingly, 26 patients (40%) initially unresectable had secondary resection (n=24) or radiotherapy (n=2) with curative intent. (409).

Targeted drugs in SRC-GC

Specific oncogenic pathways may induce specific sensitivity to targeted agents. There are no data concerning SRCC in recent trials testing targeted agents in GC. However, efficacy in diffuse type has been evaluated in a few trials.

HER2 targeting agents

Currently, human epidermal growth factor receptor 2 (HER2 is a therapeutic target in GC. *Her2* amplification or overexpression in GC or GEJ cancer is ranging from 11 to 22.1% (410–416). *HER2* overexpression is more often noted in intestinal type GC than in diffuse type or SRCC (5%) (33,410,412–414,417–423) and in the carcinoma located at proximal stomach and GEJ (24-35%) than in the remaining stomach (9.5% to 21%) (33,417–420).

Pronostic value of HER2 positive status is still controversial but is generally associated with poor outcomes or aggressive disease (410,412–414,416,418–421,424–427). However, some studies found a favorable (411,428) or no association (429–432) with prognostic of HER2 overexpression in GC. Of note, some authors found that *HER2* overexpression might have an unfavorable prognostic factor in the intestinal subtype but not in the diffuse one (419,430). However, other studies found that *HER2* status is associated with poor prognostic in both intestinal and diffuse subtypes (413).

The International ToGA phase III trial showed that the humanized monoclonal antibody against HER2, Trastuzumab, when combined with CT (capecitabine or 5-FU and cisplatin), could prolong OS in *HER2* positive AGC or GEA compared to CT alone. This effect correlated with level of *HER2* protein overexpression (417). Of note, the sub-group analysis among patients with a diffuse-type tumor showed no benefit to the adjunct of trastuzumab but the number was small (n=25 vs. n=26).

In SRC GC, the diagnosis of *HER2* status by immuno-histochemistry is more difficult to perform due to the marginalised cytoplasm and nucleus, leading to misinterpretation of strong non-specific staining (433–438). A Korean study found more than 50% of trastuzumab-resistance among 13 SRC GC HER2+ and low *HER2*

amplification index was an independent molecular predictors for trastuzumab resistance in multivariate analysis (439). It remains however, recommended to test routinely all patients with GC for the *HER2* status at the initial diagnosis regardless of histological type (415,417,435) but other studies are necessary to assess the real benefit on SRC GC.

To conclude, in SRCC, (i) HER2 is rarely positive, (ii) HER2 testing is more challeging, and (iii) there are some arguments suggesting that anti-HER2 efficacy would be less. However, at present is is not recommended to take into acount histological type to administrate anti-HER2 therapy.

Anti-angiogenic agents

A randomized, double-blind, placebo-controlled phase III study (AVAGAST) evaluated the effect on OS of bevacizumab (a humanized anti-VEGF monoclonal antibody) in combination with CT (fluoropyrimidin-cisplatin) as first-line therapy in unresectable locally advanced or metastatic gastric or GEJ adenocarcinoma. Although AVAGAST did not reach its primary objective (10.1 months in the placebo arm vs. 12.1 months in the bevacizumab arm p=0.1002), adding bevacizumab to CT was associated with significant increases in progression-free survival and overall response rate (440). An unplanned analysis of the AVAGAST study suggested a benefit in the subset of non-Asians with diffuse histologic type (HR=0.68; 95%CI=0.48-0.97) (441). These data need to be confirmed in prospective studies specifically targeting this population.

The phase III trial (REGARDS), tested ramucirumab, an anti-VEGF-R2 antibody, versus best supportive care after first-line platinum-containing or fluoropyrimidine-containing CT in advanced gastric or GEJ adenocarcinoma. Ramucirumab provided a significant benefit in OS (5.2 vs. 3.8 months, HR=0.78; *p*=0.047) (442). In subgroup analysis, a high benefit was found in the diffuse type (HR = 0.56; 95%CI: 0.36-0.85), but not in the intestinal one (HR = 1.009, 95%CI: 0.583-1.745), suggesting higher sensitivity to anti-angiogenics. Conversely, in the RAINBOW trial testing ramucirumab in combination with paclitaxel in second line, the OS benefit concerned only the intestinal histological subtype (HR: 0.705 (0·534–0·932) (443).

Supplemental data are needed to elucidate those controversial results of anti angiogenic in patients with diffuse type tumor. At present no data regarding SRC has been published.

Other targeted drugs

Anti-EGFR (epidermal growh factor receptor)

EGFR expression has been showed as an independent predictor of poor prognosis in patients with SRC GC but not for those with non-SRCC suggesting a potential difference according to histological type (98). Data from the EXPAND and REAL3 studies suggest that addition of EGFR antibodies to CT does not convey additional benefit for patients with advanced gastric and GEJ adenocarcinoma (444,445). Anti-EGFR may even be harmfull in diffuse type tumors since, a subgroup analysis found a HR for OS of 1.44 (1.01–2.03) in defavor of the Anti-EGFR arm (444).

Mammalian target of rapamycin (mTOR) inhibitors

The mTOR inhibitors seem interesting from a biological point of view. Indeed, phospho-mTOR is expressed in 60% of intestinal and 64% of diffuse-type GC (446). Everolimus, an oral mTOR inhibitor, was evaluated in an international phase III in previously treated AGC (447). Median OS was not improved by everolimus compared to best supportive care (5.4 months *vs.* 4.3 months, HR=0.90; *p*=0.124). The subgroup analysis showed no benefit of everolimus for the diffuse-type GC.

Immunotherapy

Among novel molecules in development in GEA, checkpoint inhibitors are probably the most promising. Preclinical data suggest that PD-L1 expression is significantly upregulated following *Helicobacter pylori* infection and that the resulting decrease in T-cell proliferation can be reversed by anti-PD-L1 antibodies (448). PD-L1 is expressed in 30.1 to 63% of GC whereas it is undetectable in normal gastric mucosal tissue in healthy subjects (68,449–456). PD-L1 is overexpressed in about 23-27% of cases of gastric or GEJ SRCC (451,457). SRC-GC showed more PD-1(+) immune cells than other histological types (63,6%, p= 0.019) (451). PD-1 expression has been associated with a poor prognosis and a higher rate of recurrence (RR of 2.43, p=0.012) and is correlated with PD-L1 expression in patients with GC (458). There are conflicting reports with regard to PD-L1 expression and prognosis in GC (68,451–456,458,459). Checkpoint inhibitors demonstrated clinical benefit in patients with advanced and refractory GC (456). As

observed in other tumor types, PD-L1 expression is associated with a higher response rate to checkpoint inhibitors (460).

In the KEYNOTE-012 trial, Pembrolizumab, an anti-PD1 monoclonal antibody, was administered monotherapy in 39 recurrent or metastatic gastric or GEJ adenocarcinoma patients with PD-L1 expression. Most patients have received ≥ 2 priors CT regimens. An encouraging overall response rate of 22 % was observed with a 6-month OS rate of 69 % (456). A randomised, double-blind, placebo-controlled, phase 3 trial (ATTRACTION-2) tested Nivolumab in patients with advanced gastric or GEJ cancer refractory to, or intolerant of, at least two previous CT. The survival benefits indicate that nivolumab might be a new treatment option with a specific effect in the intestinal group (n=175, HR for OS: 0.59 (0·41–0·85)) in contrast to diffuse histologic type (n=169, HR: 0.82 (0·57–1·17)) (461).

Other locations

Colorectal

Generalities

SRC constitutes approximately 1% of colorectal cancer (CRC) cases (25,462–471). Its incidence in Indian subcontinent has been reported to be higher with no clear explanation (472). Discrepencies exist about SRC-CRC location but it tends to affect more frequently the right hemicolon (24,25,464,466–469,473–480).

Similarly with SRC GC, SRC-CRC (i) is uniformly associated with younger patients populations, (ii) has a later stage of presentation, (iii) has a higher incidence of scirrhous carcinoma, (iv) has a higher risk of peritoneal dissemination at diagnosis or at recurrence (up to 50%-75% of risk in the course of the disease and more frequently for colon than for rectal location, (v) has a higher rik of LNM, (vi) has a lower risk of liver metastases, and (vii) is associated with worse outcomes compared to non–SRC-CRC (all retrospective studies) (11,24,25,463,464,466–471,473–475,478–490).

Rectal SRC-CRC seem to have better survival than colon SRC-CRC (472). At the difference of GC that typically metastasies either within peritoneum or haematogenically and seldom by both routes (491), metastatic SRC-CRC (mSRC-CRC) frequently occur by both routes (466).

Several studies found that CRC with minor component of SRC (<50%) were similar to those of SRC-CRC in terms of molecular features (492), clinicopathological characteristics (including metastatic spreading) and prognosis (480,481,493). Of note, mucinous adenocarcinoma carry a poorer prognostic if they contain SRC (479,494,495).

Molecular data

From the molecular point of view and contrary to SRC-GC, SRC-CRC has been associated with peculiar genomic changes such as MSI-high (up to 40%), high-frequency of CpG island methylator phenotype, higher methylation level of long interspersed nucleotide element-1 and frequent BRAF mutation and low COX-2 expression (465,492,496–498). Due to high frequency of MSI-high mutations and associated poor prognosis, tumors with SRC morphology in patients who are less than 60 years of age are to be screened for MSI-high mutations as per revised Bethesda guidelines in 2002 (499) in

order to allow familial screening and an access to access immunotherapy in metastatic cases (500).

Treatment adaptation

A Dutch nationwide population-based study has shown no significant interaction between SRC-CRC and adjuvant CT efficacy, suggesting a comparable benefit from adjuvant CT in non-SRC-CRC and SRC-CRC (474).

Based on the SEER database, Ling and al. found preoperative RT as an independent prognostic factor associated with improved survival in 142 patients with stage III rectal SRCC (470). SRCC responds well to radiation, thus, whenever indicated, neoadjuvant radiation should be included in the treatment protocol for rectal SRCC (501).

Fu and al. evaluated retrospectively from SEER database, the interest of surgery for mSRC-CRC (94 patients) compared to non-mSRC-CRC (3,474 patients) and found a poorer prognosis for SRC-CRC group (median survival time: 17 vs 29 months, $p<0.001$) (493). Moreover, they showed a higher rate of invalid surgery (defined as recurrence or death within 6 months after undergoing tumor resection) in the SRC-CRC group compared to the non-SRC-CRC group (24,5% vs 13%, $p<0,001$).

Peritoneal carcinomatosis

Kwakman and al. recently published a meta-analysis assessing prognostic clinicopathological parameters after CRS and HIPEC in patients with peritoneal carcinomatosis from CRC. Only 3 studies (299 patients) reported sufficient information to include SRC histology. Pooled analysis showed a negative effect on survival of SRC histology (HR: 2.01, $p=0.003$) with no heterogeneity ($p=0.85$) (502). Other studies reported similar findings (483,484,502–507).

Despite this dismal prognosis, patients with SRC-CRC may benefit from CRS and HIPEC in a highly selected subgroup in which CCR0 is achievable (500).

Esophagus

Epidemiology

The incidence of esophageal SRCC (SRC-EC) is estimated to range from 3.5% to 12.4% for all esophageal adenocarcinoma (26,508–511) with a striking male predominance (85%) that differs from SRC-GC (510).

Influence of SRC component on prognosis

Few studies assessed specifically SRC-EC, but similarly to GC, SRC-EC portend a worse prognosis (26,509,511–516). Nafteux et al. also found that SRC-EC (with a minor or major component of SRC) (n=114) had worse overall cancer-specific 5-year survival than other adenocarcinoma of the esophagus (n=806) after primary surgery (22.4% vs. 59.3%, p<0.0001). However, after adjustement on confunding factors, only the presence of a major component of SRC was an independent predictor of poor prognosis (509). These findings underline the importance of evaluating the SRC component in terms of prognosis.

The presence of SRC in the diagnostic biopsy sample has been reported to be a good predictor for the presence of >50% of SRC in GC with an accuracy of 92.5% (127). In the esophagus, data are more conflicting. Those results are in accordance with those of a previous study in GEJ and esophageal adenocarcinoma in which concordance between pretherapeutic biopsies and the final histologic findings was extremely high (90.6%) (513). However, in this study the SRC and mucinous histology were mixed together, and the definitions of the histologic groups based on the major histopathologic component was not specified. Another study recently published by Nafteux et al. found differrent results with a positive predictive value to predict the presence of SRC > 50% in only 43,9% (509).

Therapeutic adaptation

Few studies assessed specifically SRC-EC, but similarly to GC. SRC-EC respond less to radio/chemotherapy compared to non SRC EC (26,509,511–516).

Because of the suspected chemoresistance of SRC histology, an alternative treatment strategy for locally advanced SRC-EC is consideration of neoadjuvant CRT (517). Because of the suspected chemoresistance of SRC histology in esogastric cancer from the ADCI001 study (14), our group evaluated in a dedicted study primary surgery (n=74) versus neoadjuvant CRT (n=23) in clinical stage III esophageal and GEJ SRC

(518). Wherease tumors were comparable regarding clinical prestagging, there was evidence of significant tumoral ($p<0.003$), nodal ($p<0.001$), and pTNM ($p<0.001$) downstaging in the CRT group. Three-year OS was significantly improved (51% vs. 21%, $p=0.002$), with decreased disease recurrence (30.4% vs. 59.5%, $p=0.015$). In multivariate analysis the sole independent favorable prognostic factor identified was the administration of neoadjuvant CRT (HR: 0.41, $p=0.02$). Likewise, Chirieac et al. showed that patients with esophageal or GEJ adenocarcinoma who have SRC or mucinous histology benefited substantially from preoperative CRT before performing esophagectomy with a similar benefit (513). Another study from the SEER database suggested a benefit with the use of RT (before or after surgery) for SRC-EC (511).

Despite benefit on neoadjuvant CRT in SRC-EC, several studies found that those tumors responded however less favorably to this therapeutic scheme than non SRC-EC (512,514,515) with (i) a lower rate of clinical response (512) , (ii) a lower rate of pCR (514,515) (and (iii) worse OS and DFS (515) either with platinum (512,514,515) or taxan-based regimen (512,515).

Other locations

Other locations were mostly reported under the form of case reports and concern the appendix, the breast, the bladder, the ovaries, the gallbladder, the prostate, the lung (519–525).

Interestingly, a population based study of the SEER database focused on SRCC regardless of tumor location and compared prognosis according to tumor location. Inclusion criteria were pathological diagnosis of SRCC (using histology code: 8490/3) and primary site SRCC with ≥200 patients in 1988-2012 period. Multivariate analyses showed that the primary tumor location was an independent prognostic factor of survival. When compared to SRC-GC, patients with breast and SRC-CRC had a better cause-specific survival (CSS); patients with lung, small intestine, or bladder SRCC had similar CSS, whereas esophageal, gallbladder, and pancreatic SRCC had a poorer (150).

Conclusion

The great heterogeneity of GC, the frequent coexistence of several tumor components, the multiplicity of pathological classifications and the recent advent of molecular classifications make more complex the study of GC.

The histological definition of SRCC which is now included in PCCC in the latest WHO classification has changed over time and mainly correspond to genomically stable tumors. Evaluation of the SRC component appears to be of prognostic interest. The prognostic value of SRCC is still debated but seems dependent on the stage of the disease: better or equivalent prognosis in the case of superficial cancer and worse prognosis a higher risk of LNM, PC and margins invasion in more advanced tumor. These characteristics are also found in extra gastric tumor sites.

These elements suggest the need for an adaptation of initial staging (mandatory staging laparoscopy) and treatment with (i) restricted indication in endoscopic treatment, (ii) adaptation of the surgical procedure especially in terms of margins.

Nevertheless, current data are insufficient to recommend a specific therapeutic strategy with a high level of evidence. The place of intraperitoneal treatments (HIPEC, PIPAC) are being evaluated. Several studies have raised chemoresistance of SRCC. The results of the PRODIGE19 phase II trial evaluating the interest of primary surgery versus perioperative CT in SRCC are pending. Preliminary data suggest better FLOT efficacy compared to ECF in SRCC.

The individualization of SRCC in current and future trials will lead to propose a suitable therapeutic strategy in order to improve patient prognosis.

Conclusion générale

La grande hétérogénéité des adénocarcinomes gastriques avec la coexistence fréquente de plusieurs contingents tumoraux, l'existence de plusieurs classifications anatomopathologiques et l'avènement récent des classifications moléculalires en fait une pathologie complexe à étudier.

La définition histologique de l'adénocarcinome à cellules indépendantes (ADCI) qui est maintenant incluse dans les adénocarcinomes à cellules isolées dans la dernière classification OMS. Celle-ci a été évolutive au cours du temps et correspond sur le plan moléculaire essentiellement aux tumeurs génomiquement stables. L'évaluation du contingent tumoral à cellules indépendantes semble d'intérêt sur le plan pronostique. Cette valeur pronostique reste toujours débattue mais paraît dépendante du stade de la maladie : pronostic meilleur ou équivalent en cas de cancer superficiel et pronostic plus péjoratif avec un tropisme ganglionnaire et péritonéal marqué et un risque d'envahissement des marges longitudinales majoré en cas de tumeur plus évoluée. Ces caractéristiques sont également retrouvées dans les localisations tumorales extra gastriques.

Ces éléments suggèrent la nécessité d'une adaptation du bilan (coelioscopie exploratrice systématique) et du traitement avec (i) des indications de traitement endoscopique restreintes, (ii) une adaptation du geste chirurgical notamment en terme de marges.

Néanmoins, les données actuelles ne sont pas suffisantes pour recommander avec un haut niveau de preuve une prise en charge spécifique de cette pathologie La place des traitements intra-péritonéaux (CHIP, PIPAC) est en cours d'évaluation. Plusieurs études ont évoqué une chimiorésistance des ADCI. Les résultats de l'essai de phase II PRODIGE19 évaluant l'intérêt d'un changement de stratégie dans les ADCI sont en attente. Des données préliminaires suggèrent une meilleure efficacité du FLOT par rapport à l'ECF dans les ADCI.

L'individualisation des ADCI dans les essais en cours et futurs permettra d'évaluer la nécessité de proposer une stratégie thérapeutique adaptée afin d'essayer d'améliorer la survie des patients.

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Titre de la Thèse: Adénocarcinome à cellules peu cohésives: revue exhaustive de la littérature.

Thèse - Médecine - Lille 2018

Cadre de classement: Chirurgie viscérale et digestive

DES + spécialité: Chirurgie générale + Chirurgie viscérale et digestive

Mots-clés: ADCI, gastrique, entité distincte, pronostic, chimiorésistance

Résumé:

Introduction: Alors que l'incidence du cancer de l'estomac décroit depuis les dernières décennies, celle de l'adénocarcinome à cellules indépendantes (ADCI) est en constante augmentation. Ce type histologique individualisé dans la classification OMS semble avoir des caractéristiques distinctes des autres types d'adénocarcinomes gastriques. Le but de cette revue était de réaliser une mise au point sur les données publiées sur l'ADCI gastrique principalement mais aussi dans les autres localisations, notamment colorectale et oesophagienne.

Méthode: Une revue exhaustive de la littérature publiée en langue Anglaise entre 1980 et avril 2018 a été réalisée en utilisant les termes suivants: "signet ring cell carcinoma", "poorly cohesive cells", "Laurén and diffuse type", "linitis plastica" et "Borrmann type IV".

Résultats: La définition histologique de l'ADCI a été évolutive au cours du temps et correspond sur le plan moléculaire essentiellement aux tumeurs génomiquement stable. L'évaluation du contingent tumoral à cellules indépendantes semble d'intérêt sur le plan pronostique. Cette valeur pronostique reste toujours débattue mais paraît dépendante du stade de la maladie: pronostic meilleur ou équivalent en cas de cancer superficiel et pronostic plus péjoratif avec un tropisme ganglionnaire et péritonéal marqué et un risque d'envahissement des marges longitudinales majoré en cas de tumeur plus évoluée. Ces caractéristiques sont également retrouvées dans les localisations tumorales extra gastriques. Ces éléments suggèrent la nécessité d'une adaptation du bilan (coelioscopie exploratrice systématique) et du traitement avec (i) des indications de traitement endoscopique restreintes, (ii) une adaptation du geste chirurgical notamment en terme de marges. La place des traitements intra-péritonéaux (CHIP, PIPAC) est en cours d'évaluation. Plusieurs études ont évoqué une chimiorésistance des ADCI. Les résultats de l'essai de phase II PRODIGE19 évaluant l'intérêt d'un changement de stratégie dans les ADCI sont en attente. Des données préliminaires suggèrent une meilleure efficacité du FLOT par rapport à l'ECF dans les ADCI.

Conclusion: L'ADCI est une entité histologique individualisée dont les caractéristiques sont distinctes des autres types d'adénocarcinomes. L'individualisation des ADCI dans les essais en cours et futurs permettra d'évaluer la nécessité de proposer une stratégie thérapeutique adaptée afin d'essayer d'améliorer la survie des patients.

Composition du Jury:

Président: Professeur G. PIESSEN

Assesseurs: Professeur E. LETEURTRE, Professeur A. ADENIS, Docteur J. BRANCHE