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RESPONSIBLE EDITORS FOR THIS ISSUE

Poorly cohesive cells gastric carcinoma including signet-ring cell cancer: Updated review of definition, classification and therapeutic management

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Abstract

While the incidence of gastric cancer (GC) in general has decreased worldwide in recent decades, the incidence of diffuse cancer historically comprising poorly cohesive cells-GC (PCC-GC) and including signet ring cell cancer is rising. Literature concerning PCC-GC is scarce and unclear, mostly due to a large variety of historically used definitions and classifications. Compared to other histological subtypes of GC, PCC-GC is nevertheless characterized by a distinct set of epidemiological, histological and clinical features which require a specific diagnostic and therapeutic approach. The aim of this review was to provide an update on the definition, classification and therapeutic strategies of PCC-GC. We

focus on the updated histological definition of PCC-GC, along with its implications on future treatment strategies and study design. Also, specific considerations in the diagnostic management are discussed. Finally, the impact of some recent developments in the therapeutic management of GC in general such as the recently validated taxane-based regimens (5-Fluorouracil, leucovorin, oxaliplatin and docetaxel), the use of hyperthermic intraperitoneal chemotherapy as well as pressurized intraperitoneal aerosol chemotherapy and targeted therapy have been reviewed in depth for their relative importance for PCC-GC in particular.

Key Words: Poorly cohesive cells gastric carcinoma; Review; Definition; Classification; Therapeutic management

Core Tip: Although the worldwide incidence of gastric cancer (GC) has decreased in recent decades, the incidence of diffuse cancer historically comprising poorly cohesive cells-GC (PCC-GC) and including signet ring cell cancer is rising. While the existing literature concerning PCC-GC is scarce, this narrative review aims to provide an update on the classification and management of PCC-GC in light of several recent developments: (1) The updated definition according to World Health Organization classification and Verona consensus; (2) An update in curative approaches following the recent validation of 5-Fluorouracil, leucovorin, oxaliplatin and docetaxel regimen and development of hyperthermic intraperitoneal chemotherapy; and (3) Role of chemotherapy and targeted therapies in the treatment of PCC-GC.

INTRODUCTION

Worldwide, gastric cancer (GC) is ranked as the 5th most frequently diagnosed cancer. Because of its poor prognosis, it is responsible for the 3rd highest cancer-related death rate[1]. Despite a global decline in the overall incidence of GC, the relative incidence of diffuse-type GC historically comprising poorly cohesive cells-GC (PCC-GC) and including signet ring cell (SRC) cancer has shown a steady increase in the past few decades, especially in the United States and Europe[2-4]. Based on data from the Surveillance, Epidemiology and End Results (SEER) database, collected between 1973 and 2000, an increase of 400% of the diffuse type GC has been noted[4]. In contrast to other histological types of GC, SRC-GC is known to be associated with a younger age at the time of diagnosis along with a more female sex distribution[5-8]. Since the publication of the first edition of the World Health Organization (WHO) classification of GC in 1977, the definition of SRC-GC has changed several times until the 5th edition in 2019[9-13]. Before 2010, SRC-GC was classified as a separate specific subtype of GC[9,10,13]. In the edition of 2010, the SRC-GC category was redefined entirely as a subtype of PCC-GC[10]. Previously, alternative classification systems such as the Lauren and the Ming classification, categorized SRC-GC as 'diffuse/mixed' and 'infiltrative' type carcinoma, respectively[14,15]. As such, these multiple definitions and classifications render correct assessment and comparison of this histological subtype in the current literature challenging to make. In this context, an updated review on PCC-GC was needed to address the following topics: (1) Recent definition according to WHO classification[12] and Verona consensus [16]; (2) Update in curative approaches following validation of the new perioperative chemotherapy (CT) regimen 5-Fluorouracil, leucovorin, oxaliplatin and docetaxel (FLOT)[17,18] and the increasing role of hyperthermic intraperitoneal chemotherapy (HIPEC) in the prevention of, or as a curative treatment for, peritoneal metastases; and (3) Recent developments in future-based therapeutic strategies including CT, pressurized intraperitoneal aerosol chemotherapy (PIPAC) and targeted therapies including immunotherapy.

LITERATURE SEARCH

A literature search in the MEDLINE/PubMed and *Reference Citation Analysis* (https://www.referencecitationanalysis.com/) database was conducted with the use of the following search terms: 'Signet

ring cell carcinoma' (*n* = 3345), 'PCC' (*n* = 136), 'Lauren and diffuse type' (*n* = 257), 'linitis plastica' (*n* = 423) and 'Bormann type IV' (*n* = 178) up to 2021. Only studies in the English language published after January 1980 were eligible for inclusion. Studies were screened based on the abstract. Additional studies were retrieved by screening the references of each article. Case reports and studies including patients < 18-years-old were excluded as well as studies reporting on non-gastric PCC-GC. Studies reporting on < 30 cases were also excluded. Abstracts and meeting reports were only included if the information was found to be relevant enough in the context of the subject. Studies were only included after the agreement of both VD and GP.

OVERVIEW AND UPDATE ON HISTOLOGICAL AND MOLECULAR CLASSIFICATIONS

Overview and update on histological and molecular classifications of SRC- and PCC-GC.

The most commonly used classifications in GC are the WHO and the Laurén classifications[10,11,14].

WHO and Verona classification

The WHO definition of SRC-GC and-more recently-PCC-GC has evolved in function of the different published editions of the WHO classification. In the very first edition, published in 1977, SRC-GC was considered as a separate subtype of GC and was defined as 'a tumor which contained more than 50% of isolated or small groups of malignant cells containing intracytoplasmic mucin'. As such, four morpho-logical SRC types were defined[9]. By the time the 3rd edition of the WHO classification was published in 2000, this was extended to 5 morphological SRC types[11]. In the 4th edition in 2010, the SRC-GC category was completely redefined as a subtype of PCC-GC[10]. PCC-GC is composed of neoplastic cells that are isolated or arranged in small aggregates without well-formed glands. The definition of the extent of SRC to qualify as SRC-GC evolved to "predominantly" or "exclusively" in the 4th and 5th editions of the WHO[10,12]. SRCs are characterized by a central optically clear, globoid droplet of cytoplasmic mucin with an eccentrically placed nucleus[10]. Other cellular subtypes not fulfilling the requirements of this definition should be defined as PCC not otherwise specified (PCC-NOS). PCC-NOS include tumors composed of neoplastic cells resembling histiocytes or lymphocytes; others have deeply eosinophilic cytoplasm; some PCC are pleomorphic with bizarre nuclei. A mixture of the different cell types can be seen, including a mixture of PCC-NOS and SRC. Historically, mucinous adenocarcinoma has frequently been misclassified as SRCC due to the frequent observation of SRC in this subtype[19, 20]. Overall, this added a lot of confusion in analyzing data from the literature.

Invited by the European chapter of the International Gastric Cancer Association (IGCA), a multidisciplinary expert panel convened in 2017 with the intent to clarify the pathological definition of PCC-GC[16]. In a consented conclusion, it was proposed that only PCC-GC with more than 90% of cells representing an SRC morphology should be classified as SRC-type. The two other categories were PCC with SRC component (< 90% but > 10% of SRC) and PCC-NOS: < 10% of SRC[16]. An overview of the proposed definition and classification is shown in Table 1 and Figure 1. On another level, this newly defined classification also incorporates the theory that the extent of SRC in the tumor may be an expression of the differentiation grade of PCC[16]. The importance of this consensus definition cannot be underestimated since it will enable future studies to standardize results and facilitate comparison between studies in order to avoid the major heterogeneity that has characterized studies concerning SRC-GC for the past few decades.

Laurén and other classifications

The Laurén classification, which is the oldest and most general classification, categorizes tumors into two major categories: Intestinal-type tumors, characterized by cohesive neoplastic cells organized in well-differentiated glandular structures and diffuse tumors, diffusely infiltrating the gastric wall, with little to no gland formation. The latter type consists of PCCs, with or without SRC morphology and thus corresponds most with the PCC category of the WHO classification[14]. Comparative studies are shown in Table 2. Tumors exhibiting features of both the intestinal and diffuse types (> 25% of either component) are designated as mixed-type adenocarcinoma and account for approximately 10% of all gastric adenocarcinomas[21,22]. Some tumors may be unclassified. Although widely implemented, the Laurén classification does not allow for any clinical or pathological evaluation according to the proportion of the SRC component, which is an additional justification for the implementation of the recently proposed renewed definition of PCC by the WHO[12] and the European chapter of IGCA[16].

The original Japanese classification system categorized GC into differentiated and undifferentiated tumors, with undifferentiated type corresponding to diffuse type[23]. A more recent version of the classification proposed by the Japanese Gastric Cancer Association (JCGA) is however mainly based on the WHO classification and distinguishes between papillary, tubular, poorly differentiated and mucinous adenocarcinoma as well as SRC tumors[24]. Finally, the Ming classification describes an expanding and infiltrative type, the latter being strongly correlated to diffuse type[25,26].

Table 1 Subcategories of poorly cohesive cell carcinoma as proposed by the Verona consensus[16] in two recent clinical studies[47,48]

Ref.	Category of PCC		
	SRC type: > 90% of Signet Ring cells	PCC with SRC component: < 90% but > 10% of SRC	PCC-NOS: < 10% of SRC
Bencivenga *et al*[47]	32 (18.5)	98 (56.6)	43 (24.9)
Roviello *et al*[48]	0 (0)	87 (60.8)	56 (39.2)

PCC: Poorly cohesive cell; SRC: Signet ring cells; NOS: Not otherwise specified.

Table 2 Concordance rates between World Health Organization and Laurén classification systems

Ref.	Reclassification of SRC and PCC-GC according to Laurén classification			
	n	% Intestinal	% Diffuse	% Mixed
Pyo *et al*[7], 2016	3170	0.6	96.3	3.1
Pyo *et al*[173], 2017	5309	0.0	96.1	3.9
Wanebo *et al*[174],1993	187	2	87	11
Hass *et al*[175], 2011	160	7.6	66.2	26.2
Lee *et al*[176], 2012	320	0.0	90.6	9.4
Heger *et al*[58], 2014	235	0.0	75.3	20.0
Chon *et al*[53], 2017	1646	1.2	96.4	2.4

SRC: Signet ring cells; PCC: Poorly cohesive cells; GC: Gastric cancer.
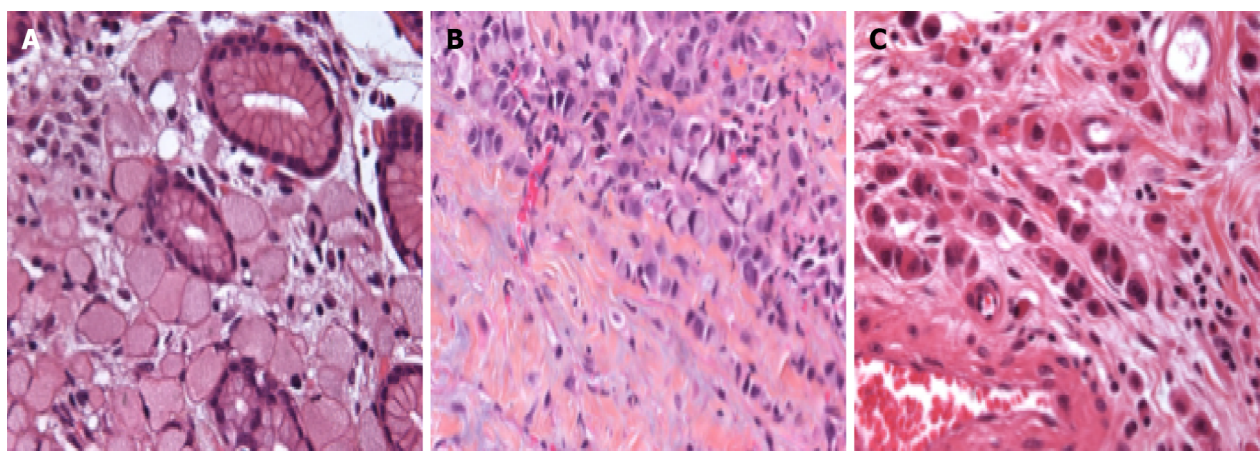
DOI: 10.4251/wjgo.v14.i8.1406 **Copyright** ©The Author(s) 2022.

Figure 1 Subcategories of poorly cohesive cell gastric carcinoma as proposed by the European consensus meeting of the European Chapter of International Gastric Cancer Association (Verona, 2017). A: Signet ring cells type (SRC): > 90% of SRC; B: Poorly cohesive cell (PCC) with SRC component: < 90% but > 10% of SRC; C: PCC-non other specified: < 10% of SRC.

Linitis plastica

Linitis plastica (LP) is macroscopically described as an increased thickening and rigidity of the gastric wall with an aspect of linen. From a histological point of view, it corresponds to involvement of the entire stomach wall by carcinoma cells, mostly SRC, with a very abundant sclerous stroma. LP is an uncommon variant of gastric adenocarcinoma occurring in 7%–17.4% of cases[27-31]. LP is rarely individualized in studies for two main reasons; (1) Some authors confuse the histological and macroscopical definition[32-34] assimilating SRC-GC with LP, thus adding to the confusion; and (2) LP is also referred to as Borrmann type IV or scirrhous gastric carcinoma in the Eastern literature. An illustration of gastric LP is presented in Figure 2. In one study at our center, among 159 patients with SRC-GC and non-SRC_GC, LP occurred in 35.6% in the SRC group *vs* 6% in the non-SRCC group (*P* < 0.001)[35]. Most LP in the non-SRC-group had a minor component of SRC. In other words, LP and SRCC
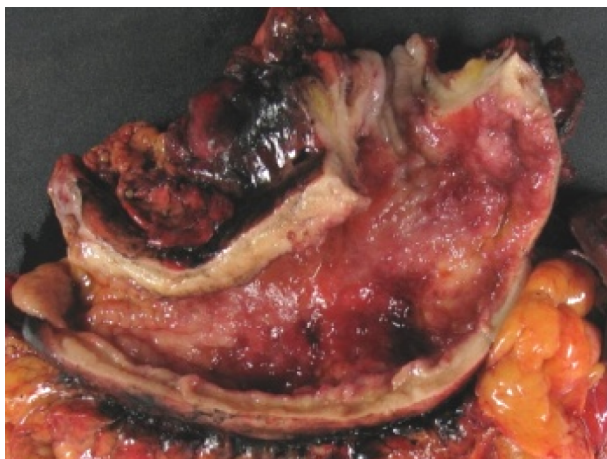
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Figure 2 A macroscopic view of a gastric linitis plastica.

are not synonyms[36] but are closely associated. However, we believe that the current definition of SCR-GC should be used systematically. The term 'linitis plastica' can be additionally used when applicable.

Molecular characteristics

From a molecular point of view, GC has been classified into four genomic subtypes in a landmark project by The Cancer Genome Atlas[37]. These four subtypes comprise: (1) The Epstein-Barr virus (EBV) subtype (9%), characterized by extreme DNA hypermethylation, recurrent PIK3CA mutations and amplification of JAK2, programmed death-ligand 1 (PD-L1) and PD-L2; (2) The microsatellite instability (MSI) subtype (21%), containing mutations in genes encoding for targetable oncogenic signaling proteins and associated with a more favorable oncological outcome; (3) A genomically stable (GS) subtype (20%), in which most but not all PCC-GC are categorized; and (4) The chromosomal instability (CIN) subtype (50%), associated with aneuploidy and amplification of genes involved in receptor tyrosine kinase/RAS/MAPK signaling[38]. More recently, another molecular analysis for GC identified four subgroups of tumors associated with distinct clinical outcomes: (1) A mesenchymal-type, including diffuse-subtype tumors and most PCC-GC tumors; (2) An MSI subtype, characterized by numerous mutations and a better prognosis; (3) A tumor protein 53 (TP53)-active subtype, associated with higher rates of EBV infection; and (4) A TP53-inactive subtype, similar to the CIN subgroup[39]. The importance of these molecular classifications cannot be underestimated as they provide a roadmap for patient stratification. In addition to the prognostic impact, it has been proven that these genomic subtypes are associated with distinct features regarding tumor response. As such, this subtype classification is primordial in the implementation of current and future clinical trials that evaluate the role of targeted therapies, among others[40,41]. However, we have to bear in mind that GC consists of heterogeneous tumors and that several histological and molecular components can be present in the same tumor and may be modified by the treatment applied[42]. In addition, there is no strict correlation between the histological types and molecular subtypes. PCC-GC are mostly GS but can also be MSI or EBV type with potential therapeutic implications since both molecular subtypes are associated with response to immune checkpoint inhibitors[43].

Prognostic features of PCC-GC

All stages studies: Although most studies agree about the poor prognosis of diffuse GC according to the Laurén classification, more discrepancies exist about the specific prognosis of PCC-GC[22,35,44,45]. An overview of studies reporting on the prognosis of all stages of SRC- and PCC-GC, is shown in Table 3. The reported prognosis of PCC-GC in Western studies is in general worse compared to that of most Eastern studies with, however, significant differences in terms of tumor stages; the majority of studies in early gastric cancer (EGC) (*i.e.* GC pT1a or pT1b regardless of lymph node status)[46] originate from Eastern series.

Among PCC tumors, the prognostic impact of the relative percentages of an SRC component within the tumors remains controversial[40]. Two studies evaluated the prognostic role of the Verona consensus with marked differences between the distribution of the three categories questioning the reproducibility of the classification (Table 1)[40,47,48]. Bencivenga *et al*[47] showed that the percentage of SRC was associated with tumor stage and survival in PCC-GC: The percentage of SRC was inversely related to tumor aggressiveness, pT stage ($P < 0.001$) and the number of positive nodes coded as a continuous variable ($P = 0.009$). Long-term survival was significantly higher in SRC-type (> 90% SRC) compared with PCC with SRC component (< 90% but > 10% of SRC) and PCC-NOS (< 10% of SRC) tumors[47]. In the other study, on pathological revision no patients with SRC-type (> 90% SRC) were

Table 3 Summary of studies reporting the all-stage prognostic value of signet ring cell- and poorly cohesive cell-gastric cancer

Ref.	n	n SRC-CG (%)	% LNM	5-yr survival rate %, SR-CGC *vs* other	Univariate	Multivariate	Compared to
Eastern studies							
Maehara *et al*[49], 1992	1500	51 (3.4)	33.3	74.5 *vs* 52.4	*P* < 0.01	-	Non SRC-GC
Kim *et al*[177], 1994	3702	450 (12.2)	50.6	59.7 *vs* 57.7/48.6/43.1	NS	-	WD/MD/PD
Otsuji *et al*[178], 1998	1498	154 (10.3)	27.9	68.2 *vs* 43.9 (10-yr survival rate)	*P* < 0.05	-	Non SRC-GC
Yokota *et al*[179], 1998	923	93 (10.1)	43	Worse	NS	-	Non SRC-GC
Kim *et al*[180], 2004	2358	204 (8.7)	26.5	60.2 *vs* 48.9	*P* < 0.01	NS	Non SRC-GC
Park *et al*[181], 2008	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[a]	WD/PD/MC
Zhang *et al*[45], 2010	1439	218 (15.1)	76.1	44.9 *vs* 36	*P* = 0.013	NS	Non SRC-GC
Chiu *et al*[182], 2011	2439	505 (20.7)	53.7	57.6 *vs* 56	NS	-	Non SRC-GC
Jiang *et al*[55], 2011	1439	211 (14.7)	52,0	49.8 *vs* 41.4	*P* = 0.001	-	Non SRC-GC
Lee *et al*[176], 2012	1002	320 (31.9)	37.2	84.8 *vs* 71.9/57.8	*P* < 0.001	NS	PD/MC
Kwon *et al*[50], 2014	769	108 (14.0)	43.5	55.4 *vs* 64.5/46.2 (10-yr survival rate)	*P* < 0.001	NS	WD-MD/PD-MC
Liu *et al*[162], 2015	1464	138 (9.4)	30.4	36.2 *vs* 49.5	*P* < 0.001	*P* < 0.001	Non SRC-GC
Chon *et al*[53], 2017	7667	1646 (21.5)	25.8	80.0 *vs* 70.0 (10-y survival rate)	*P* < 0.001	NS	WMD/PD
Lu *et al*[183], 2016	2199	354 (16.1)	-	15.9 mo *vs* 22.1 mo	*P* = 0.002	< 0.001	Non SRC-GC
Western studies							
Theuer *et al*[184], 1999	3020	453 (15.0)	NR	Similar	NS	NS	Non SRC-GC
Piessen *et al*[35], 2009	180	59 (32.8)	83.1	28 *vs* 46	*P* = 0.004	*P* = 0.004	Non SRC-GC
Taghavi *et al*[44], 2012	10246	2666 (26)	59.7	Similar (Disease-specific survival)	NS	*P* = 0.15	Non SRC-GC
Bamboat *et al*[51], 2014	569	210 (36.9)	61.0	49 *vs* 24/43 (5-y cumulative-mortality)	*P* < 0.0001	-	WMD/PD
Postlewait *et al* [6], 2015	768	312 (40.6)	66.3	33.7 mo *vs* 46.6 mo (OS)	*P* = 0.011	NS	Non SRC-GC
Voron *et al*[8], 2016	1799	899 (50)	73.2	26 mo *vs* 51 mo (median survival)	*P* < 0.001	*P* < 0.041	Non SRC-GC

[a]The survival rate of patients with stage IV signet ring cells-gastric cancer was poorer than those with the other three types.

LNM: Lymph node metastasis; SRC-GC: Signet ring cells-gastric cancer; non SRC-GC: gastric cancer other types than SRC-GC; WMD: Well-and moderately-differentiated gastric cancer; PD: Poorly differentiated; MC: Mucinous cancer; NS: Non-significant.

identified[48]. The 5-year overall survival (OS) was significantly higher in PCC with an SRC component (< 90% but > 10% of SRC) compared with PCC-NOS (< 10% of SRC) (63.3% *vs* 12.7%)[48].

EGC: An overview of studies reporting on the prognostic outcomes of SRC- or PCC-EGC is shown in Table 4. Most studies demonstrated that the prognosis of SRC- or PCC-EGC is similar to or even better than that of other EGC[49-52]. The largest of these studies, including data on 3272 patients, concluded that the prognosis of SRC-EGC was better than that of well-and moderately-differentiated EGC [hazard ratio (HR) for OS = 0.66, 95%CI: 0.44-0.98][53]. In one of the few Western studies, Gronnier *et al*[54] showed that SRC-EGC was associated with a 5 year-OS benefit (85% *vs* 76%, *P* = 0.035) compared to

Table 4 Summary of studies reporting prognostic value of signet ring cell- and poorly cohesive cell-early gastric cancer

Ref.	*n*	*n* SRC-GC (%)	% LNM	5-yr survival rate %, SRC-GC *vs* other	Univariate	Multivariate	Compared to
Eastern studies							
Maehara *et al*[49], 1992	384	28 (7.3)	10.7	100 *vs* 94.8	NS	-	Non SRC-GC
Kim *et al*[177], 1994	785	185 (23.6)	7.6	92.9 *vs* 83.9/87.3/93.6	NS	-	WD/MD/PD
Otsuji *et al*[178], 1998	568	94 (16.5)	5.3	93 *vs* 76.3	*P* < 0.05	-	Non SRC-GC
Yokota *et al*[179], 1998	253	41 (16.2)	-	Similar	NS	-	Non SRC-GC
Hyung *et al*[80], 2002	933	263 (28.2)	5.7	94.2 *vs* 91.6	*P* = 0.01	-	Non SRC-GC
Kim *et al*[180], 2004	561	94 (16.8)	2.1	96.3 *vs* 90.8	NS	NS	Non SRC-GC
Kunisaki *et al* [185], 2004	513	120 (23.4)	9.2	Better	*P* = 0.033	*P* = 0.036	Non SRC-GC
Ha *et al*[186], 2008	1520	388 (25.5)	9.5	99.7 *vs* 99.1/97.2	NS/*P* = 0.019	-	WMD-PA/PD-MC
Zhang *et al*[45], 2010	138	49 (35.5)	-	Similar	NS	-	Non SRC-GC
Chiu *et al*[182], 2011	579	149 (25.7)	10.7	96.1 *vs* 89.6	*P* = 0.01	-	Non SRC-GC
Jiang *et al*[55], 2011	269	54 (20.1)	16.7	94.3 *vs* 90.6	*P* = 0.007	*P* = 0.011	Non SRC-GC
Kwon *et al*[50], 2014	326	51 (15.6)	9.8	84.0 *vs* 76.0/65.7 (10-yr survival rate)	NS	-	WD-MD/PD-MC
Kim *et al*[52], 2014	2085	345 (16.5)	9.0%	Similar (disease-related survival)	NS	-	WD/MD/PD
Wang *et al*[187], 2015	334	115 (34.4)	8.5	93.9 *vs* 85.8	*P* = 0.027	0.001	UD
Chon *et al*[53], 2017	3272	1091 (33.3)	-	95 *vs* 85 (10-yr survival rate)	*P* < 0.001	*P* = 0.041 (WMD)	WMD-PD
Imamura *et al* [188], 2016	746	152 (20.4)	2.0	97.4 *vs* 89.9	*P* = 0.012	*P* = 0.038	Non SRC-GC
Western studies							
Gronnier *et al*[54], 2013	421	104 (24.7)	24,0	85 *vs* 76	*P* = 0.035	NS	Non SRC-GC
Bamboat *et al*[51], 2014	437	174 (39.8)	-	0 *vs* 8/24 (5-disease-specific mortality)	*P* = 0.001	-	WMD/PD

EGC: Early gastric cancer; LNM: Lymph node metastasis; SRC-GC: Signet ring cells-gastric cancer; non SRC-GC: Gastric cancer other types than SRC-GC; WMD: Well-and moderately-differentiated gastric cancer; PD: Poorly differentiated; MC: Mucinous cancer; NS: Non-significant.

non-SRCEGC, although SRC-EGC was more frequently associated with submucosal invasion[54]. However, the survival benefit in this study was no longer objectivated after multivariable analysis, possibly because of the lower rate of non-cancer-related deaths in the younger SRC group. More studies in Western populations are required to validate further the superior prognostic results of PCC- or SRC-EGC as reported by the Eastern series and should include an analysis according to the new WHO classification and Verona consensus[12,16].

Advanced GC (GC invading beyond the submucosa)
Table 5 presents an overview of studies reporting on the prognostic characteristics of SRC- or PCC-advanced GC (AGC). At an advanced stage, SRC-AGC is associated with deeper tumor invasion, a higher rate of lymph node involvement, an increased potential for diffuse infiltration of the gastric wall (LP), a greater risk of metastatic peritoneal disease, lower rates of R0 resection and higher rates of early disease recurrence[44,55-57]. Whether the dismal prognosis of PCC-GC is related to a more advanced stage of the disease at the time of diagnosis or to inherently more aggressive tumor biology is much debated[35,44]. Results from a large population-based study in the United States demonstrated that

Table 5 Summary of studies reporting prognostic value of signet ring cell- and poorly cohesive cell-gastric cancer

Studies	n	n SRC (%)	% LNM	5-yr survival rate % (PCC-GC *vs* other)	Univariate	Multivariate	Compared to
Eastern studies							
Maehara *et al* [49], 1992	1116	23 (2.1)	60.8	42.5 *vs* 37.6	NS	-	Non SRC-GC
Kim *et al*[177], 1994	2917	265 (9.1)	80.8	33 *vs* 45.4/38.8/35.3	*P* < 0.05	-	WD/MD/PD
Otsuji *et al*[178], 1998	930	60 (6.4)	63.3	44.4 *vs* 27.5 (10-yr survival rate)	NS	-	Non SRC-GC
Yokota *et al*[179], 1998	430	52 (12.1)	-	Worse	NS	-	Non SRC-GC
Kunisaki *et al* [185], 2004	600	54 (9.0)	57.4	Similar	NS	-	Non SRC-GC
Kim *et al*[180], 2004	1797	110 (6.1)	47.3	35.1 *vs* 39.5	NS	-	Non SRC-GC
Li *et al*[56], 2007	4759	662 (13.9)	75.7	42.4 *vs* 50.1	0.009	NS	Non SRC-GC
Chiu *et al*[182], 2011	1860	356 (19.1)	71.6	41.5 *vs* 46.3	*P* = 0.018	-	Non SRC-GC
Jiang *et al*[55], 2011	2046	157 (7.7)	64.3	31.5 *vs* 35.7	NS	NS	Non SRC-GC
Zu *et al*[57], 2014	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 *et al*[50], 2014	443	57 (12.9)	73.7	26.0 *vs* 50.5/38.4 (10-yr survival rate)	*P* = 0.044	NS	WD-MD/PD-MC
Chon *et al*[53], 2017	1777	555 (31.2)	-	53 *vs* 58/52 (10-yr survival rate)	*P* < 0.001	*P* < 0.001	WMD/PD
Western studies							
Heger *et al*[58], 2014	723	235 (32.5)	63.0	26.3 *vs* 46.6 mo (median survival)	*P* < 0.001	*P* = 0.02 (backward analysis)	Non SRC-GC

EGC: Early gastric cancer; LNM: Lymph node metastasis; SRC-GC: Signet ring cell-gastric cancer; PCC-GC: Poorly cohesive cells-gastric cancer; WMD: Well-and moderately-differentiated gastric cancer; PD: Poorly differentiated; MC: Mucinous cancer; NS: Non-significant.

after adjustment for stage, SRC histology was not independently associated with a worse prognosis[44]. These findings seem to be confirmed by several other studies that reported a worse prognosis in univariable analysis, but not in multivariable analysis after adjustment for tumor stage[6,56-58]. Critics, however, state that a posteriori adjustment by multivariable analysis results in an oversimplification of the issue. In the absence of any possibility for prospective randomization, some authors noted that a matched case-control analysis should be the methodological tool of choice to clarify this debate[59]. Piessen *et al*[35] confirmed that SRC histology entailed a worse stage-independent prognosis in patients with GC than other histological subtypes[35].

The underlying factors that may cause the discrepancy between the prognostic characteristics of early and advanced PCC-GC remain uncertain. This topic is even more complicated by the geographical differences and potential variability in the molecular tumor characteristics between Western and Eastern populations[60]. Within the group of GCs, early and advanced PCC-GC may represent two distinct entities, each with its own prognostic features[61].

Pre-therapeutic evaluation in PCC-GC

A thorough anamnestic evaluation with emphasis on family history should be performed to detect clinical criteria for hereditary diffuse GC[62]. Because the tumoral spread in PCC-GC mainly occurs within the deeper tissue layers, mostly in the absence of any mucosal alterations, conventional endoscopy and superficial biopsies may miss the diagnosis. Repeated endoscopies should consequently be performed with deep biopsies guided by endoscopic ultrasonography. A CT scan can give useful additional information by identifying areas of the stomach characterized by an increased wall thickness in the case of LP.

In light of the WHO criteria from 2000 for SRC-GC (*i.e.* more than 50% SRC), the overall reliability of pretherapeutic biopsies to predict specimen histology has been evaluated. Among 254 patients, the presence of SRC in routine pre-therapeutic endoscopic biopsies could accurately predict SRC histology

and its associated poor prognosis (Sensitivity: 88.1%, Specificity: 95.4%, Positive predictive value: 92.7%, Negative predictive value: 92.4%)[5]. Future studies evaluating the concordance between pretherapeutic biopsies and specimens in PCC-GC will have to be performed using the new WHO definition and the Verona consensus[12,16].

Positron emission tomography (PET) imaging using fluoro-2-deoxy-D-glucose (FDG) may be helpful to eliminate distant metastases in the case of advanced disease[63,64]. However, PCC-GC has proven to be associated with a lower PET sensitivity and a lower standard uptake value (SUV) than no PCC-GC, with a potential risk of false-negative results[65-67]. In addition, two studies suggested that a higher SUVmax was a predictive factor of poor prognosis in SRC histology[68,69].

Staging laparoscopy is currently recommended by the European Society for Medical Oncology (ESMO) for tumors ≥ stage Ib[70] and by the National Comprehensive Cancer Network (NCCN) for tumors ≥ T1b[71]. Several studies reported high rates of peritoneal carcinomatosis (5%-21%) discovered during surgical exploration after a standard workup, including CT scan in advanced PCC-GC or diffuse tumors[35,72-74]. In the PlASTIC-study, comparing staging laparoscopy and FDG-PET/CT in preoperative workup of locally AGC, treatment intent changed from curative to palliative in 73 patients (19%) after staging laparoscopy (detecting peritoneal or locally non-resectable disease) *vs* in 12 patients (3%) after FDG-PET/CT (detecting distant metastases)[74]. This risk was 1.5 to 3 times higher than in other tumors[35,74]. Staging laparoscopy has been consequently proposed as an essential tool for pretherapeutic evaluation of PCC-GC[75]. In addition to a complete and systematic exploration of the abdominal cavity, staging laparoscopy provides the possibility to perform a peritoneal lavage with cytology. A positive cytology classifies the disease as stage IV, necessitating a change in therapeutic strategy[30,76,77]. Alternative procedures such as laparo-endoscopic single-site surgery are currently being evaluated to optimize the detection of peritoneal disease. Even with standard staging laparoscopy, lesions on the mesenteric side of the small bowel are still frequently missed[78,79]. A small periumbilical incision to explore the small bowel by means of palpation may be helpful in advanced PCC-GC.

Curative treatment

Endoscopic resection: An increasing amount of evidence has been gathered that endoscopic treatment using an endoscopic submucosal dissection could represent a valid option for non-ulcerated undifferentiated lesions, ≤ 2 cm in diameter, limited to the mucosa and without LVI[50,80-82]. Lesions in this category are currently excluded from the absolute indication by the JGCA recommendations due to the lack of sufficient evidence for long-term outcome. Still, they may in the future be included pending the results of the JCOG1009/1010 study[83]. For Western countries, the European Organisation for Research and Treatment of Cancer has defined the indications for endoscopic resection for EGC during the St. Gallen international consensus meeting. For diffuse EGC, gastrectomy is considered mandatory[84]. In the NCCN and ESMO guidelines, undifferentiated tumors (including PC-GC) are contra-indicated for endoscopic treatment[71].

Surgery: Multiple studies have demonstrated a higher risk of positive resection margins due to the specific infiltrative characteristics of PCC-GC and a higher risk of lymph node involvement[6,8,35]. Consequently, some surgical specificities should be proposed.

According to the JCGA, a proximal margin of 5 cm is recommended in cases of AGC with an infiltrative growth pattern (*i.e.* PCC-GC). A frozen section is advisable in case of doubt. For EGC, a gross resection margin of 2 cm should be respected[83]. A margin of 4 cm is recommended by the NCCN regardless of histological type[71]. According to the ESMO guidelines, a subtotal gastrectomy is indicated if a macroscopic proximal margin of 5 cm can be achieved. For diffuse GC and consequently PCC-GC, a margin of 8 cm should be respected. If not, a total gastrectomy is advised[70]. In the case of an antropyloric location of PCC-GC, a frozen section of the distal margin should be proposed since there is a significant risk of duodenal invasion due to submucosal and subserosal spreading of the tumor[40].

Neither JCGA nor ESMO, nor NCCN guidelines advocate a modification of the D2 Lymphadenectomy without systematic splenectomy for AGC in PCC-GC[70,71,83]. Only the guidelines of the Italian Research Group for Gastric Cancer recommend a D2+ lymphadenectomy (D2 + stations 8p, 12p/b, 13, station 14 v along the mesenteric vein and para-aortic lymph node station 16a2/16b1) for tumors classified as diffuse-type according to the Laurén classification and located in the distal two-thirds of the stomach[85]. Whether or not the extent of lymphadenectomy should be adapted to the higher potential of lymph node metastasis in PCC-GC is questionable and has so far not been investigated by any randomised controlled trial (RCT).

Impact of PCC-GC in peri-operative CT

In Western countries, before the FLOT era: The added value of perioperative CT for GC has been demonstrated in two randomized trials[17,86,87]. Perioperative CT allows for an increased R0-resection rate, tumor- and lymph node downstaging and significant improvement in OS. In a post hoc analysis of the MAGIC trial, no statistically significant difference in pathological response rate could be identified between the different histological types according to the Lauren classification. Of note, only 18 % of included patients presented with diffuse-type GC and SRC-presence was not specifically evaluated[88].

Other studies, mainly retrospective, have suggested that Laurén diffuse-type GC and SRC-GC specifically were less chemosensitive than other histological subtypes[8,89-92]. In a large multicentric retrospective cohort study among 1050 patients with SRC-GC defined as tumors with > 50% SRC, Messager *et al*[92] found that perioperative CT (ECF or 5FU/Cisplatin) did not result in tumor- or lymph node downstaging, nor did it entail any benefit in terms of R0 resection[92]. Perioperative administration of CT was even identified as an independent factor of poor prognosis in the SRC-GC group (HR = 1.4, 95%CI: 1.1-1.9). Several hypotheses could account for these findings: (1) Innate chemoresistance of SRC-GC; (2) Disease progression during neoadjuvant CT; or (3) Toxicity resulting in relative immunodepression with subsequent facilitation of disease progression[93]. The results found by Messager *et al*[92] highlighted the urgent need for a randomized controlled trial dedicated to identifying optimal therapeutic strategies in the management of SRC-GC. In this context, the phase II/III PRODIGE 19 randomized controlled trial was designed to evaluate whether upfront surgery with adjuvant CT (6 cycles of ECF regimen) would provide a survival benefit compared to perioperative CT (perioperative ECF regimen) in patients with stage Ib-III SRC-GC[94]. The phase II study met its primary endpoint of > 26 mo of 2-year OS in the upfront surgery + adjuvant CT arm. However, 2-year OS rates were 60% in the perioperative arm *vs* 53.5% in the upfront surgery arm, with a median survival of 39 mo *vs* 28 mo respectively (exploratory HR = 0.71, 95%CI: 0.40-2.64). Subsequently, phase III was not launched[18].

Another retrospective study, including 235 patients with SRC-GC, defined as tumors with any percentage of SRC, suggested that SRC-GC had a lower clinical (21.1% *vs* 33.7%, *P* = 0.001) and histopathological (16.3% *vs* 28.9%, *P* < 0.001) response rate to neoadjuvant CT than non-SRC-GC[58]. However, within the cohort of SRC-GC patients that displayed a clinical or histopathological response, the outcome was favorable which led to the conclusion that perioperative CT should not be abandoned for SRC-GC. In the same study, the addition of a taxane-based CT regimen did not have any positive influence on prognosis in SRC-GC patients.

In Western countries in the FLOT era: Taxane-based CT regimens and more specifically the FLOT regimen, have in recent years proven their added value in the peri-operative treatment of GC[17,95,96]. Results concerning the benefit of the FLOT regimen in the treatment of PCC-GC remain, however, controversial: Homan *et al*[97] found that the pathological complete response rate to FLOT-therapy in intestinal-type GC was higher as compared to diffuse/mixed type GC (30.8% *vs* 0%, *P* < 0.05)[97]. Likewise, in the phase II NeoFLOT study, it was demonstrated that when considering near-complete responders (< 10% residual tumor), 85% had an intestinal-type GC in contrast to only 10% and 5% of these patients that exhibited a diffuse and mixed type tumor, respectively[98]. However, the results from the FLOT4 trial demonstrated a beneficiary treatment effect of the FLOT regimen *vs* ECF regardless of histological type and presence of an SRC component[17]. The definition of SRC in the FLOT trial, was the presence of any SRC in the pathological report, which does not correlate with the recent definition of PCC-GC[12]. The beneficial effect on OS was more pronounced in the SRC-GC than in diffuse GC. These findings are difficult to analyze in the absence of pathological reassessment of the pathological specimen. However, this was an additional argument not to launch the phase III of PRODIGE 19 trial.

In Eastern countries: In Eastern countries where primary surgery followed by adjuvant CT is the standard treatment, three trials evaluating preoperative CT dedicated to LP have been identified[99-102]. The first study with S1 (JCOG02) did not reach its expected survival rate and consequently, no phase III study was performed; the second study with S1+ cisplatin showed interesting tumor response (JOG0210) but did not show any superiority of the neoadjuvant arm in the long term in the phase III (JCOG0501).

Impact of PCC-GC on adjuvant CT: In Eastern countries, adjuvant CT is the preferred therapeutic strategy in GC based on two major trials: The ACTS-GC (Adjuvant CT Trial of TS-1 for GC) trial and the CLASSIC study with CAPOX[103,104]. There was no subgroup analysis based on diffuse or SRC-GC type in both trials. However, in the ACTS-GC trial, the S-1 setting had a significant favorable HR for death in the undifferentiated group (that includes PCC-GC) compared to surgery alone, contrary to the differentiated group, where the effect was not significant[103]. After 5 years, the results were maintained in both subgroups[105]. A retrospective study suggested no tumor response of SRC-GC to either oxaliplatin or docetaxel adjuvant-based CT. In contrast, the mixed SRC-GC group responded to both regimens with even more improved survival with the docetaxel-based regimen[90]. Although the exact definition of SRC-GC and mixed SRC-GC was not mentioned in this study, it supports the fact that PCC-GC could behave differently according to the percentage of SRC and underlines the potential benefit of taxane-based CT in PCC-GC.

Impact of PCC-GC on adjuvant radiotherapy: Several RCT's evaluated the potential benefit of adjuvant CRT in GC (Intergroup 0116, ARTIST, ARTIST2, CRITICS)[106-110]. They failed to show a favorable outcome in PCC or diffuse GC subgroups. An analysis of the SEER database using a propensity score however showed favorable outcome of adjuvant RT in patients with diffuse-type GC (median survival time: 30 mo with adjuvant RT *vs* 18 mo without adjuvant RT, *P* < 0.001, HR: 0.75, *P* < 0.001). A major bias was the absence of data regarding the use of CT[111].

Impact of PCC-GC on neo adjuvant chemoradiotherapy: Phase III trials evaluating RT or preoperative CRT in GC, excluding the gastroesophageal junction (GEJ), are scarce and small[112-114]. Several phase II trials showed encouraging results in tumor response and survival but this type of strategy has so far been limited by the related toxicity[115-119]. At least two trials are ongoing: TOPGEAR[120] and CRITICS-II[121] with a planned subgroup analysis according to histological type in the CRITICS-II study.

A study analyzing 107 localized GA (n = 45 non-SRC-GC and n = 62 SRC-GC) treated with preoperative CRT showed that the presence of SRC was associated with a lower rate of pCR (11% *vs* 36%, P = 0.004) which remained significant even with a low percentage of SRC (1%–10%; P = 0.014). The higher the fraction of SRC, the lower the probability of pCR (P = 0.03). Poorly differentiated and SRCC led to shorter OS (P = 0.046 and P = 0.038, respectively)[89].

Impact of PCC-GC in intraperitoneal chemotherapy combined with surgery

Preventive setting: The high failure rate of surgical curative therapy for GC and PCC-GC in particular, is mainly due to a high rate of peritoneal recurrence. In this context, a strategy of preventive intraperitoneal chemotherapy (IPC) during the surgical intervention has been hypothesized. Two meta-analyses (including mostly Asian studies) showed a clear benefit of preventive IPC in terms of survival[122,123]. However, no subgroup analysis for PCC-GC was performed. The phase III GASTRICHIP trial (NCT01882933) is currently evaluating the role of oxaliplatin-based HIPEC in addition to curative gastrectomy in patients with GC or Siewert II/III cardia adenocarcinoma with either serosal infiltration, LN positivity, positive peritoneal cytology or perforated tumor. Stratification according to the presence of SRC on pretherapeutic biopsies, has been anticipated[124]. The ongoing PREVENT trial (FLOT-9) (NCT04447352) is a multicenter, randomized, controlled, open-label study including a total of 200 patients with localized and locally advanced non-metastatic diffuse or mixed type (Laurens's classification) adenocarcinoma of the stomach and Type II/III esogastric junction tumors. Patients undergo perioperative FLOT and are randomized between curative gastrectomy alone and curative gastrectomy + intra operative cisplatin-based HIPEC[125]. In Japan, the PHOENIX-GC2 Trial will evaluate the impact of IPC as adjuvant or perioperative CT for patients with type 4 scirrhous GC in addition to S1 CT [126].

Curative setting: In a curative setting, cytoreductive surgery (CRS) plus HIPEC has been strongly recommended for AGC by a panel of international experts[127,128]. However, controversy concerning this topic remains, with further high-quality evidence being expected to confirm the value of this treatment strategy, which could be of particular interest for PCC-GC.

At present, no published RCT has compared CRS + HIPEC *vs* CT alone. Two ongoing randomized phase III trials evaluate the role of surgery in limited- metastatic adenocarcinoma of the stomach or esophagogastric junction in patients responding to CT and will include patients with peritoneal carcinomatosis[129,130]. In the RENAISSANCE trial no stratification based on histological type has been anticipated and HIPEC is not described in the protocol (NCT02578368)[129].In the SURGIGAST trial, stratification based on histological type (PCC-GC on biopsy) has been anticipated (NCT03042169)[130].

In the multicenter, open-label, phase III PERISCOPE II trial, patients with peritoneal metastasis are currently randomized between CT alone *vs* CRS + HIPEC with CT. Study completion is expected by October 2022[131]. Stratification based on the main histological subtype (diffuse *vs* intestinal) has been anticipated.

Based upon the available evidence, it is presumed that for GC in general, only patients with a peritoneal cancer index (PCI) < 12, who display a clinical response after neoadjuvant CT and in whom no diffuse bowel involvement is found, may benefit from the added value of CRS + HIPEC[132,133]. For PCC-GC, little to no specific selection criteria have been proposed so far. In a retrospective study on 89 patients, Chia *et al*[134] demonstrated that after treatment with CRS + HIPEC, non-PCC-GC patients had a better OS (21.8 mo *vs* 13.2 mo, P = 0.0214) compared to PCC-GC patients. The authors suggested that if complete CRS was achievable in patients with a PCI < 7, the presence of an SRC component should not be considered as a contra-indication for CRS + HIPEC[134].

In 2018, Bonnot *et al*[135] published the results from the large multicenter retrospective CYTO-CHIP study, which evaluated the survival results of CRS compared to CRS + HIPEC in patients with AGC with peritoneal involvement[135]. Only patients with a complete CRS (CC-0 or CC-1) were included in the study. After propensity scored weighting, this study showed that CRS + HIPEC was associated with an increased OS and the potential of disease eradication compared to CRS alone. Subgroup analysis confirmed the superiority of CRS + HIPEC in patients with PCC-GC defined according to WHO classification[11]. An ancillary study recently published showed that PCC-GC was associated with poorer OS (HR: 0.43, P = 0.003), as were pN3, PCI, and resection with a completeness of cytoreduction score of 1, whereas HIPEC was associated with improved OS (HR: 0.52; P < 0.001). The benefit of CRS-HIPEC over CRS alone was consistent, irrespective of histology, with a median OS of 16.7 mo *vs* 11.3 mo (HR: 0.60, P = 0.018) in the PCC-GC group, and 34.5 mo *vs* 14.3 mo (HR: 0.43, P = 0.003) in the non-PCC-GC group. Non PCC-GC and HIPEC were independently associated with improved recurrence-free survival and fewer peritoneal recurrences. In patients who underwent HIPEC, PCI values < 7 and < 13 were

predictive of OS in PCC-GC and non PCC-GC populations, respectively[136]. Consequently, those patients should be well-selected to avoid the excess morbidity rate associated with an unnecessary exploratory laparotomy[137].

Role of PCC-GC on non-curative treatments

CT: Several studies demonstrated that SRC-GC had different infiltrative and metastatic mechanisms than non-SRC-CG. It lacked free ribosomes but were rich in lysosomes and mucus impeding anticancer drugs from getting to the cell[20,138]. In a metastatic setting, there are few data concerning the chemosensitivity of PCC-GC. Rougier *et al*[139] 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 linitis plastic or SRC histology (*P* = 0.003 and *P* = 0.16, respectively)[139].

A retrospective analysis of the FLAGS trial suggested that survival was improved among patients with advanced diffuse GC treated with S-1 and cisplatin compared to 5-FU and cisplatin[140]. A dedicated phase III trial compared both regimens in patients with metastatic diffuse gastric and GEJ adenocarcinoma previously untreated[141]. However, both regimens were similar in efficacy and safety and the primary endpoint was not met. 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 or locally advanced non-resectable gastric or GEJ SRC-GC including 17 LP. This regimen gave an interesting response rate of 66% with an OS of 14.3 mo. Interestingly, 26 patients (40%) initially unresectable had secondary resection (*n* = 24) or radiotherapy (*n* = 2) with curative intent[142].

PIPAC: PIPAC is a recently developed promising technique that allows for homogeneous loco-regional application of intraperitoneal CT at lower doses than achievable in conventional HIPEC[143]. This technique could offer a valuable alternative for patients with unresectable peritoneal disease from GC and with PCI-scores that are considered as too high for CRS + HIPEC (PCI > 7 or 12 depending on histological type). Several retrospective studies have evaluated the feasibility of this technique on patients with unresectable peritoneal metastasis from GC. The majority of patients included in these studies were affected by an SRC histology and the results show that PIPAC treatment (with low-dose cisplatin + doxorubicin) is associated with improved survival, without compromising the quality of life [143-145]. Further results from the randomized controlled multicenter phase II PIPAC EstoK 01 trial evaluated the interest of PIPAC in addition to intravenous CT and are awaited[143].

Targeted drugs in gastric SRCC: Due to some specific oncogenic pathways in GC, the efficacy of several targeted agents has been tested in recent trials, in which SRC histology has only rarely been the subject of subanalysis. On the other hand, diffuse type GC has been evaluated frequently within these trials.

Human epidermal growth factor receptor 2 targeting agents: The incidence of human epidermal growth factor receptor 2 (HER2) amplification in GC ranges from 12% to 22.1%. It is more often noted in intestinal GC than diffuse-type GC and characterized by a more frequent location in the proximal stomach and gastroesophageal junction[146-150]. Although still controversial, HER2 positive status is, in general, associated with a poor outcome and more aggressive disease[147,149,150]. Some authors found that the unfavorable prognostic value of HER2 positivity was present in intestinal-type GC, but not in diffuse-type GC[151,152]. In PCC-GC, the diagnosis of HER2 status can be somewhat troublesome due to the presence of a marginalized cytoplasm and nucleus, entailing a frequent misinterpretation of intense, non-specific staining[153-155]. The phase III ToGa trial demonstrated the added value of the humanized monoclonal antibody against HER2 (Trastuzumab) in combination with CT (capecitabine or 5-FU and cisplatin) compared to CT alone in HER2-positive AGC[156]. Of note, a sub-group analysis among patients with a diffuse-type tumor showed no benefit of trastuzumab, although the number of patients in this sub-analysis was quite low. A Korean study found resistance to trastuzumab of more than 50% among 13 patients with SRC-GC who were HER2 positive, with a low HER2 amplification index being identified as an independent molecular predictor for trastuzumab resistance in a multivariate analysis[157]. Despite these findings, it remains recommended to routinely test all patients with GC for HER2 amplification, regardless of the histological type[146,156,158]. Future studies are required to investigate more profoundly a potential benefit of trastuzumab in PCC-GC.

Anti-angiogenic agents: The randomized phase III AVAGAST trial evaluated the effect of bevacizumab [a humanized anti-vascular endothelial growth factor (VEGF) monoclonal antibody] in combination with CT (fluoropyrimidine-cisplatin) as first-line therapy in AGC. Although AVAGAST did not reach its primary objective (OS of 10.1 mo in the placebo arm *vs* 12.1 mo in the bevacizumab arm, *P* = 0.1002), the addition of bevacizumab to CT was found to be associated with a significant increase in progression-free survival (PFS) and overall response rate[159]. An additional analysis according to disease subtype, suggested a benefit of bevacizumab in a subset of non-Asian patients with the diffuse histologic type (HR = 0.68; 95%CI: 0.48-0.97)[159]. The phase III REGARDS trial compared ramucirumab (an anti-VEGF-R2 antibody) *vs* best supportive care after first-line platinum-containing or fluoropyrimidine-containing CT in AGC or gastro-esophageal junction adenocarcinoma. Ramucirumab provided a significant benefit in terms of OS (5.2 mo *vs* 3.8 mo, HR = 0.78, 95%CI: 0.603-0.998)[160]. In subgroup analysis, a significant benefit was found for diffuse-type GC (HR = 0.56; 95%CI: 0.36-0.85), but not for

the intestinal-type (HR = 1.009, 95%CI: 0.583-1.745), suggesting a higher sensitivity to anti-angiogenics. Conversely, the RAINBOW trial showed that for ramucirumab in combination with paclitaxel in a second-line treatment, the OS benefit concerned only the intestinal histological subtype [HR: 0.705 (0.534–0.932)][161]. Supplemental data are needed to establish the role of anti-angiogenic targeted therapies in patients with diffuse-type GC. Currently, no data concerning the role of anti-angiogenic therapies in the therapy of PCC-GC are available.

Anti-epidermal growth factor receptor: Epidermal growth factor receptor (EGFR) expression has been identified as an independent predictor of poor prognosis in patients with PCC-GC compared to non-PCC-GC patients[162]. Data from the EXPAND and REAL3 trials have suggested no additional benefit of anti-EGFR treatment in combination with CT for AGC[163,164]. In a subgroup analysis of the EXPAND trial in function of the histological subtype, it was even found that anti-EGFR could be harmful in diffuse-type tumors (HR for OS: 1.44, 95%CI: 1.01-2.03)[163].

Mammalian target of rapamycin inhibitors

Since phospho-mammalian target of rapamycin (mTOR) is expressed in 60% of intestinal and 64% of diffuse-type GC, mTOR inhibitors were considered an interesting therapeutic option from a biological point of view[165]. However, results from the phase III GRANITE-1 trial showed no benefit of everolimus (an oral mTOR-inhibitor) on OS compared to best supportive care for previously treated AGC[166]. In a subgroup analysis, no benefit in diffuse-type GC was found either.

CLDN18.2 antibody (zoltemuximab)

In advanced gastric/gastro-esophageal junction and esophageal adenocarcinoma patients expressing CLDN18.2, adding zolbetuximab to first-line EOX provided longer PFS and OS *vs* EOX alone in a phase 2 trial[167]. Interestingly, the vast majority of these populations had diffuse- or mixed type GC. Zolbetuximab is being evaluated in phase III studies based on clinical benefits observed in the overall population and in patients with moderate-to-strong CLDN18.2 expression in > 70% of tumor cells.

Immunotherapy

Among new treatment strategies for GC, immunotherapy, and more specifically, PD-L1 inhibitors have proven to be the most promising. PD-L1 is expressed in 30% to 63% of GC[168,169]. The results of the CheckMate 649 study demonstrated the superiority of nivolumab in combination with CT compared to CT alone. In a study population of patients with HER2 negative, previously untreated, unresectable advanced or metastatic GC or gastro-esophageal junction cancer, nivolumab in combination with CT (XELOX or FOLFOX) resulted in significantly improved OS and PFS *vs* CT in patients whose tumors expressed a PD-L1 combined positive score (CPS) ≥ 5 (HR for OS = 0.71, 98.4%CI: 0.59–0.86 and HR for PFS = 0.68, 98%CI: 0.56–0.81). This survival benefit was also observed in patients with a PD-L1 CPS ≥ 1 and in the all-randomized population[170]. The rate of patients with SRC-GC or diffuse tumors was close between patients with a CPS ≥ 5 and the overall population[170]. However, other studies found that in SRC histology, PD-L1 CPS > 1 was significantly less observed[171]. The question remains how the recent findings of the CheckMate 649 trial could be applied to PCC-GC. A group of specifically selected PCC-GC patients with S-I may benefit from immunotherapy. However, Hirotsu *et al*[172] reported that PCC-GC exhibits high MSI at low frequencies[172].

CONCLUSION

In contrast to GC in general, the relative incidence of PCC-GC has risen over the past few decades. PCC-GC represents a distinct pathological entity within the GC spectrum, characterized by specific epidemiological and clinical features, including younger age at presentation and a significantly worse prognosis, primarily due to peritoneal dissemination early in the disease. In light of these distinct features, the recently redefined pathological definition of PCC-GC by the WHO and the European chapter of IGCA will facilitate methodological standardization in future studies which in turn will help to identify which therapeutic strategies for GC in general apply to PCC-GC. We believe that the updated definition will help standardize future research concerning the prognostic results of SRC-ECG in Western populations and evaluate the correlation between pre-therapeutic biopsies and the final pathology result. Concerning the pre-therapeutic evaluation, the infiltrative growth pattern of PCC-GC along with early peritoneal dissemination justifies the use of repeat endoscopies with deep biopsies, CT-graphic imaging as well as systematic staging laparoscopy with peritoneal lavage. Since correct PCI determination is essential for therapeutic management, a small incision with palpation of the entire small bowel should be considered. Surgery is considered the mainstay of curative treatment for PCC-AGC. The role of the extent of the lymphadenectomy however in PCC-AGC should be evaluated in future studies. For PCC-EGC, no endoscopic treatment is currently advocated. The added value of peri-operative CT for PCC-GC with FLOT regimen is probable but should be further confirmed using histological reassessment. No

role of adjuvant radiotherapy has been demonstrated in PCC-GC. In the case of peritoneal disease, IPC using HIPEC or PIPAC offer a valuable treatment option on the condition that patients are well selected. To what extent the promising results of immunotherapy could apply to PCC-GC needs to be confirmed in future studies. PCC-GC in general requires a highly individualized diagnostic and therapeutic approach to optimize the inherent poor prognosis of this disease in the future. Molecular and genetic differentiation will be important in offering a patient-tailored therapeutic strategy.

FOOTNOTES

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