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

Vincent Drubay, Frederiek Nuytens, Florence Renaud, Antoine Adenis, Clarisse Eveno, Guillaume Piessen

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

©The Author(s) 2022. Published by Baishideng Publishing Group Inc. All rights reserved.

---

**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.

---

**Citation:** Drubay V, Nuytens F, Renaud F, Adenis A, Eveno C, Piessen G. Poorly cohesive cells gastric carcinoma including signet-ring cell cancer: Updated review of definition, classification and therapeutic management. *World J Gastrointest Oncol* 2022; 14(8): 1406-1428

**URL:** [https://www.wjgnet.com/1948-5204/full/v14/i8/1406.htm](https://www.wjgnet.com/1948-5204/full/v14/i8/1406.htm)

**DOI:** [https://dx.doi.org/10.4251/wjgo.v14.i8.1406](https://dx.doi.org/10.4251/wjgo.v14.i8.1406)

---

**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.referencitationanalysis.com/](https://www.referencitationanalysis.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 Laurèn 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 tumour which contained more than 50% of isolated or small groups of malignant cells containing intracytoplasmic mucin’. As such, four morphological SRC types were defined\[^{9}\]. By the time the 3\(^{rd}\) edition of the WHO classification was published in 2000, this was extended to 5 morphological SRC types\[^{11}\]. In the 4\(^{th}\) 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 4\(^{th}\) and 5\(^{th}\) 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.

**Laurèn and other classifications**

The Laurèn 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 Laurèn 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 (JGCA) 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[59], 2017 |                                                                       | 1646 | 1.2          | 96.4      | 2.4     |

SRC: Signet ring cells; PCC: Poorly cohesive cells; GC: Gastric cancer.

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
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/MC/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 = 0.002** | WD/MD/PD   |
| 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 46.5/46.2 (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-yr 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  |
| Fiessner 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-yr cumulative-mortality) | **P < 0.0001** | -           | WMD/PD      |
| Postleswait 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  |

*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.

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
non-SRC-GC, although SRC-EGC was more frequently associated with submucosal invasion[34]. 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 disease 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 [180], 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 [58], 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[39]. 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 pre-therapeutic 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 SCC 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 JGCA, 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 antr pyloric 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 JGCA 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 SGC-presence was not specifically evaluated [88].
Other studies, mainly retrospective, have suggested that Laurèn 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 (CEF 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 IIb-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[95]. 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 (JCOG2010) 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 SRC leading 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 GASTRICHIPI 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 pertherapeutic 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 (Lauren’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 scirrhoues 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 response 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, Bonnet 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 score 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-GC. 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 cisplatin for limits 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)[165].

**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-I 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 (zolbetuximab)**

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 diffuse-type 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-EGC 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

Author contributions: Drubay V and Nuytens F contributed to the analysis and interpretation of data, drafting the manuscript and final approval; Renaud F, Adenis A, Eveno C and Piessen G contributed to the analysis and interpretation of data, revision of the manuscript and final approval; Piessen G contributed to the design of the study, decision of publishing the paper.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

Country/Territory of origin: France

ORCID number: Vincent Drubay 0000-0001-6072-7963; Frederiek Nuytens 0000-0003-1194-0981; Florence Renaud 0000-0003-3614-1713; Antoine Adenis 0000-0003-3123-9746; Clarisse Eveno 0000-0001-8804-4029; Guillaume Piessen 0000-0001-8243-8310.

S-Editor: Fan JR
L-Editor: Filipodia
P-Editor: Fan JR

REFERENCES

1 Thrift AP, El-Serag HB. Burden of Gastric Cancer. Clin Gastroenterol Hepatol 2020; 18: 534-542 [PMID: 31362118 DOI: 10.1016/j.cgh.2019.07.045]
2 Amorosi A, Bianchi S, Buatiati E, Cipriani F, Palli D, Zampi G. Gastric cancer in a high-risk area in Italy. Histopathologic patterns according to Lauren's classification. Cancer 1988; 62: 2191-2196 [PMID: 3179931 DOI: 10.1002/1097-0142(19881115)62:10<2191::aid-cncr2820621020>3.0.co;2-5]
3 Marrelli D, Pedrazzani C, Morgiani G, Paefelli F, Coniglio A, Marchet A, Saragoni L, Giacopuzzi S, Roviello F. Italian Research Group for Gastric Cancer. Changing clinical and pathological features of gastric cancer over time. Br J Surg 2011; 98: 1273-1283 [PMID: 21560122 DOI: 10.1002/bjs.7528]
4 Henson DE, Dittus C, Younes M, Nguyen H, Albores-Saavedra J. Differential trends in the intestinal and diffuse types of gastric carcinoma in the United States, 1973-2000: increase in the signet ring cell type. Arch Pathol Lab Med 2004; 128: 765-770 [PMID: 15214826 DOI: 10.1043/1543-2165(2004)128<765:DTITIA>2.0.CO;2]
5 Piessen G, Amiel D, Messager M, Vinatier E, Leteurotte E, Triboulet JP, Mariette C. Is pretreatment endoscopic biopsy a good predictor of signet ring cell histology in gastric carcinoma? World J Surg 2012; 36: 346-354 [PMID: 22102091 DOI: 10.1007/s00268-011-1351-9]
6 Postlewait LM, Squires MH 3rd, Kooby DA, Poultsides GA, Weber SM, Bloomston M, Fields RC, Pawlik TM, Votanopoulos KI, Schmidt CR, Eizaj A, Acher AW, Worhunsky DJ, Saunders N, Swords D, Jin LX, Cho CS, Winslow ER, Cardona K, Staley CA, Maithel SK. The Prognostic Value of Signet-Ring Cell Histology in Resected Gastric Adenocarcinoma. Ann Surg Oncol 2015; 22 Suppl 3: S832-S839 [PMID: 26156656 DOI: 10.1245/s10434-015-4724-8]
7 Pyo JH, Ahn S, Lee H, Min BH, Lee JH, Shim SG, Choi MG, Sohn TS, Bae JM, Kim KM, Yeon S, Jung SH, Kim JJ, Kim S. Clinicopathological Features and Prognosis of Mixed-Type 11a Gastric Cancer Based on Lauren’s Classification. Ann Surg Oncol 2016; 23: 784-791 [PMID: 27613552 DOI: 10.1245/s10434-016-5549-9]
8 Voron T, Messager M, Duhamel A, Lefevre J, Mabrut JY, Goere D, Meunier B, Coniglio A, Cabaret C, Hemy A, Gléhen O, Mariette C, Paye F. Is signet-ring cell carcinoma a specific entity among gastric cancers? Gastric Cancer 2016; 19: 1027-1040 [PMID: 26606931 DOI: 10.1007/s10120-015-0564-2]
9 Oota K, Sobin H. Histological typing of gastric and oesophageal tumors, in international classification of tumors. WHO Editor WHO : Geneva, 1977
10 Bosman FT, Carneiro F, Hruban RH, Theise ND. WHO Classification of Tumours of the Digestive System. Fourth Edition, 2010
11 Hamilton SR, Aaltonen L. Pathology and Genetics of Tumours of the Digestive System. World Health Organization Classification of Tumours. IARC, Lyon: France, 2000
12 WHO Classification of Tumours Editorial Board (eds). Digestive system tumours. 5th ed. Lyon: IARC Press, 2019
Drubay V et al. PCC gastric carcinoma review

13 Watanabe H, Jass JR, Sobin LH (eds). Histological typing of oesophageal and gastric tumours. 2nd ed. WHO: International histological classification of tumours. Springer-Verlag, Berlin Heidelberg, 1990

14 Lauren P. The two histological main types of gastric carcinoma: Diffuse and so-called intestinal-type carcinoma. An attempt at a hiato-clinical classification. Acta Pathol Microbiol Scand 1965; 64: 31-49 [PMID: 14320673 DOI: 10.1111/ajm.1965.64.1.31]

15 Ming SC. Gastric carcinoma: A pathobiological classification. Cancer 1977; 39: 2475-2485 [PMID: 872047 DOI: 10.1002/1097-0424(19770639)39:6<2475::AID-Onc0280390626>3.0.CO;2-3]

16 Mariette C, Carneiro F, Grabsch HL, van der Post RS, Allum W, de Manzon G; European Chapter of International Gastric Cancer Association. Consensus on the pathological definition and classification of poorly cohesive gastric carcinoma. Gastric Cancer 2019; 22: 1-9 [PMID: 30167905 DOI: 10.1007/s10120-018-0068-0]

17 Al-Batran SE, Homann N, Paullig C, Goetzte TO, Meier J, Kasper S, Kopp HG, Mayer F, Haag GM, Luley K, Lingd U, Schniegel W, Pohl M, Steinhämser J, Folprecht G, Provst S, Prasnikar N, Fischbach W, Mahlbuch R, Trojan J, Koenigsma M, Martens UM, Thuss-Patience P, Egger M, Block A, Heinemann V, Illerhaus G, Moheler M, Schenk M, Kullmann F, Behringer DM, Heike M, Pink D, Teschedorfer C, Lohr C, Bernhard H, Schuch G, Rethwisch V, von Weikerthal LF, Hartmann JT, Kneba M, Daum S, Schulmn K, Jenger W, Belle S, Gaiser T, Onducu FS, Güntner M, Hozaeel W, Reichert A, Kraus T, Möning S, Bechwein WT, Schuler M, Schmalenberg H, Hofheinz RD; FLOT4-AIO Investigators. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin and docetaxel versus fluorouracil or capecitabine plus cisplatin and eprubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. Lancet 2019; 393: 1948-1957 [PMID: 30962686 DOI: 10.1016/S0140-6736(18)32557-1]

18 Eveno A, Adenis A, Bouche O, Le Malicost K, Hautefeuille V, Farouz B, Bigdaut AT, Egretue J, Meunier B, Mabro M, Carrere N, Barriere N, Ben Abdelghani M, Mauvais F, Di Fiore F, Malka D, Manfredi S, Piessen G. Adjuvant chemotherapy vs perioperative chemotherapy (CTX) for resectable gastric signet ring cell (GSC) gastric cancer: A multicenter, randomized phase II study (PRODIGE 19). J Clin Oncol 2019; 37: 4019-4019

19 Yao JC, Tseng JF, Worah S, Hess KR, Mansfield PF, Crane CH, Schriner II, Reddy S, Chiang SS, Najam A, Yu C, Giaco GG, Xie K, Wu TT, Feig BW, Pisters PW, Ajania JA. Clinicopathologic behavior of gastric adenocarcinoma in Hispanic patients: analysis of a single institution's experience over 15 years. J Clin Oncol 2005; 23: 3049-3013 [PMID: 15860869 DOI: 10.1016/J.JCO.2005.08.987]

20 Yang XF, Yang L, Mao XY, Wu DY, Zhang SM, Xin Y. Pathobiological behavior and molecular mechanism of signet ring cell carcinoma and mucinous adenocarcinoma of the stomach: a comparative study. World J Gastroenterol 2010; 16: 750-754 [PMID: 19949154 DOI: 10.3748/wjg.v10.i7.750]

21 Bringleland EA, Wasmuth HH, Mjones P, Myklebust TÅ, Gronbech JE. A population-based study on incidence rates, Lauren distribution, stage distribution, treatment, and long-term outcomes for gastric adenocarcinoma in Central Norway 2001-2011. Acta Oncol 2017; 56: 39-45 [PMID: 27710195 DOI: 10.1080/0284186X.2016.1227086]

22 Baiocchi GL, Tiberio GA, Minicozzi AM, Morgagni P, Marrelli D, Bruno L, Rosa F, Marchet A, Congilio A, Saragoni L, Veltri M, Pacelli F, Roviello F, Nitti D, Giuliani SM, De Manzon G. A multicentric Western analysis of prognostic factors in advanced, node-negative gastric cancer patients. Ann Surg 2010; 252: 70-73 [PMID: 20562603 DOI: 10.1097/SLA.0b013e3181e5855c]

23 Nakamura K, Sugano H, Takagi K. Carcinoma of the stomach in incipient phase: its histogenesis and histologic appearances. Gan 1968; 59: 251-258 [PMID: 5726267]

24 Sano T, Coit DG, Kim HH, Roviello F, Kassab P, Wittekind C, Yamamoto Y, Ohashi Y. Proposal of a new stage grouping system for gastric cancer: International Gastric Cancer Association staging project. Gastric Cancer 2017; 20: 217-225 [PMID: 26897166 DOI: 10.1007/s11786-016-0601-9]

25 Davessar K, Pizzullo JC, Kessianim N, Hale JH, Juaregui HO. Gastric adenocarcinoma: prognostic significance of several pathologic parameters and histologic classifications. Hum Pathol 1990; 21: 325-332 [PMID: 2312109 DOI: 10.1016/0046-8177(90)90234-v]

26 Luebke T, Baldus SE, Grass G, Bollschweiler E, Thiele J, Dienes HP, Hoelscher AH, Moenig SP. Histological grading in gastric cancer by Ming classification: correlation with histopathological subtypes, metastasis, and prognosis. World J Surg 2005; 29: 1422-7; discussion 1428 [PMID: 16222448 DOI: 10.1007/s00268-005-7795-z]

27 Kitamura K, Beppu R, Anai H, Ikejiri K, Yakabe S, Sugimachi K, Saku M. Clinicopathologic study of patients with Borrmann type IV gastric carcinoma. J Surg Oncol 1995; 58: 112-117 [PMID: 8449890 DOI: 10.1002/jso.2930580208]

28 Kodera Y, Ito S, Machizuki Y, Yamamura Y, Misawa K, Ohashi N, Nakayama Y, Koike M, Fujitaka M, Nakano A. The number of metastatic lymph nodes is a significant risk factor for bone metastasis and poor outcome after surgery for limitis plastica-type gastric carcinoma. World J Surg 2008; 32: 2015-2020 [PMID: 18563480 DOI: 10.1007/s00268-008-9672-z]

29 Machara V, Morigraphi S, Orita H, Kakeji Y, Haraguchi M, Kokaeda N, Sugimachi K. Lower survival rate for patients with carcinoma of the stomach of Borrmann type IV after gastric resection. Surg Gynecol Obstet 1992; 175: 13-16 [PMID: 1621194]

30 Schauer M, Peiper M, Theisen J, Knoefel W. Prognostic factors in patients with diffuse type gastric cancer (limitis plastica) after operative treatment. Eur J Med Res 2011; 16: 29-33 [PMID: 21345767 DOI: 10.1186/2047-783x-16-1-29]

31 Kim EY, Yoo HM, Song KY, Park CH. Limited significance of curative surgery in Borrmann type IV gastric cancer. Med Oncol 2016; 33: 69 [PMID: 27251378 DOI: 10.1007/s10632-016-0783-3]

32 Feng J, Al-Abbadi M, Kodali U, Dhar R. Cyto logical diagnosis of gastric limitis plastica by endoscopic ultrasonic guided fine-needle aspiration. Diagn Cytopathol 2006; 34: 177-179 [PMID: 16511853 DOI: 10.1002/dc.20382]

33 Wachtel MS, Zhang Y, Chiriva-Internati M, Frezza EE. Different regression equations relate age to the incidence of Lauren types 1 and 2 stomach cancer in the SEER database: these equations are unaffected by sex or race. BMC Cancer 2006; 6: 65 [PMID: 16539725 DOI: 10.1186/1471-2407-6-65]

34 Van Cutsen E, Sagareta X, Topal B, Haustermans K, Prenen H. Gastric cancer. Lancet 2016; 388: 2654-2664 [PMID: 27156933 DOI: 10.1016/S0140-6736(16)30545-3]

35 Piessen G, Messager M, Leteurthe E, Jean-Pierre T, Mariette C. Signet ring cell histology is an independent predictor of
poor prognosis in gastric adenocarcinoma regardless of tumoral clinical presentation. *Ann Surg* 2009; 250: 878-887 [PMID: 19855261 DOI: 10.1097/SLA.0b013e3181b21e76]

Endo K, Sakurai M, Kusumoto E, Uehara H, Yamaguchi S, Tsutsumi N, Ikejiri K. Biological significance of localized Type IV scirrhous gastric cancer. *Oncolet Leti* 2012; 3: 94-99 [PMID: 22740862 DOI: 10.3802/ol.2011.454]

Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. *Nature* 2014; 513: 202-209 [PMID: 25079317 DOI: 10.1038/nature13480]

ds Santos NR, Seruca R, Constância M, Seixas M, Sobrinho-Simões M. Microsatellite instability at multiple loci in gastric carcinoma: clinicopathologic implications and prognosis. *Gastroenterology* 1996; 110: 38-44 [PMID: 8536886 DOI: 10.1016/gast.1996.11.016]

Cristescu R, Lee J, Nebozhyn M, Kim KM, Ting JC, Wong SS, Liu J, Yue YG, Wang J, Yu K, Ye XS, Do IG, Liu S, Gong L, Fu J, Jin JG, Choi MG, Sohn TS, Lee JH, Bae JM, Kim ST, Park SH, Sohn S, Jung SH, Tan P, Chen R, Hardwick J, Kang WK, Ayers M, Hongyue D, Reinhard C, Loboda A, Kim S, Aggarwal A. Molecular analysis of gastric cancer identifies subtypes associated with distinct clinical outcomes. *Nat Med* 2015; 21: 449-456 [PMID: 25894828 DOI: 10.1038/nm.3850]

Hu B, El Hajj N, Sittler S, Lammert N, Barnes R, Meloni-Ehrig A. Gastric Cancer: Classification, histology and application of molecular pathology. *J Gastrointest Oncol* 2012; 3: 251-261 [PMID: 22943016 DOI: 10.9789/jiss.2078-6891.2012.021]

Li Z, Tan IB, Das K, Deng N, Zourdidis H, Pattison S, Chua C, Feng Z, Guan YK, Ooi CH, Ivanova T, Zhang S, Lee M, Wu J, Nigo A, Manesh S, Tan E, Teh BT, So JB, Goh LK, Boussioutas A, Lim TK, Flotow H, Tan P, Rozen SG. Identification of molecular subtypes of gastric cancer with different responses to PI3K-inase inhibitors and 5-fluorouracil. *Gastroenterology* 2013; 145: 554-565 [PMID: 23684942 DOI: 10.1053/j.gastro.2013.05.010]

Pectasides E, Stachler MD, Derks S, Liu Y, Maron S, Islam M, Alpert L, Kwak H, Kindler H, Polite B, Sharma MR, Allen RA, O’Day E, Lounnici S, Maranto M, Kanteti R, Frizpa L, Lee C, Weber C, Seita N, Xiao Y, Hart J, Nagy RJ, Kim KM, Chu MG, Min BH, Nason KS, O’Keef L, Watanabe M, Baba H, Lamman R, Agoston A, Oh D, Dunford A, Thorner AR, Ducar MD, Wollison BM, Ha YJ, Posner MC, Roggin K, Taruga K, Chang P, Hogarth K, Siddiqui U, Gelrud A, Ha G, Freeman SS, Rhoades J, Reed S, Gyduad G, Rotem D, Davison J, Inamura Y, Adalsteinsson V, Lee J, Bass AJ, Catenacci DV. Genomic Heterogeneity as a Barrier to Precision Medicine in Gastroesophageal Adenocarcinoma. *Cancer Discov* 2018; 8: 37-48 [PMID: 28978556 DOI: 10.1158/2159-8290.CD-17-0395]

Kim ST, Cristescu R, Bass AJ, Kim KM, Odegaard JJ, Kim K, Liu XQ, Cher H, Joo M, Lee M, Lee S, Park SH, Park JO, Park YS, Lim HY, Lee H, Choi M, Talasas A, Kang PS, Cheng J, Loboda A, Lee J, Kang WK. Comprehensive molecular characterization of clinical responses to PD-1 inhibition in metastatic gastric cancer. *Nat Med* 2018; 24: 1449-1458 [PMID: 3003197 DOI: 10.1038/s41598-018-0101-2]

Taghavi S, Jayarajan SN, Davey A, Willis AI. Prognostic significance of signet ring gastric cancer. *J Clin Oncol* 2012; 30: 3493-3498 [PMID: 22927530 DOI: 10.1200/JCO.2012.46.6635]

Zhang M, Zhu G, Zhang H, Gao H, Xue Y. Clinicopathologic features of gastric carcinoma with signet ring cell histology. *J Gastrointest Surg* 2010; 14: 601-606 [PMID: 20033340 DOI: 10.1007/s11605-009-1127-9]

Murakami T. Early cancer of the stomach. *World J Surg* 1979; 3: 685-692 [PMID: 532187 DOI: 10.1007/BF01654788]

Benevenga M, Treppiedi E, Verlato G, Mengardo S, Viapiano S, de Manzoni G. The amount of cells with Signet-Ring Cell morphology has a prognostic impact in poorly cohesive gastric carcinomas. *Eur J Cancer* 2018; 92 Suppl 2: S6 [DOI: 10.1016/j.ejca.2018.01.103]

Roviello F, Marano L, Ambrosio MR, Resca L, D'Ignazio A, Petrelli F, Petrelli R, Costantini M, Polonk R, Macchiarelli R, Biviano I, Marrelli D. Signet ring cell percentage in poorly cohesive gastric cancer patients: A potential novel predictor of survival. *J Gastrointest Oncol* 2022; 48: 561-569 [PMID: 34511269 DOI: 10.1016/j.jgo.2021.09.003]

Maehara Y, Sakaguchi Y, Moriguichi S, Orita H, Korenaga D, Kohnoe S, Sugimachi K. Signet ring cell carcinoma of the stomach. Cancer 1992; 69: 1645-1650 [PMID: 1312889 DOI: 10.1002/1097-0248(199204)69:7<1645::AID-CNC2820609702>3.0.CO;2-x]

Kwon KJ, Shim KN, Song EM, Choi JY, Kim SE, Jung HK, Jung SA. Clinicopathological characteristics and prognosis of signet ring cell carcinoma of the stomach. *Gastric Cancer* 2014; 17: 43-53 [PMID: 23389081 DOI: 10.1007/s11188-013-0324-4]

Bambozat ZM, Tang LH, Vinuela E, Ku D, Gonen M, Shah MA, Brennan MF, Coti DG, Strong VE. Stage-stratified prognosis of signet ring cell histology in patients undergoing curative resection for gastric adenocarcinoma. *Ann Surg Oncol* 2014; 21: 1678-1685 [PMID: 24394986 DOI: 10.1245/s10434-013-3466-8]

Kim BS, Oh ST, Yook KJ, Kim BS. Signet ring cell type and other histologic types: differing clinical course and prognosis in T1 gastric cancer. *Surgery* 2014; 155: 1030-1035 [PMID: 24792508 DOI: 10.1016/j.surg.2013.08.016]

Chun HJ, Hyung WJ, Kim C, Park S, Kim JH, Park CH, Ahn JB, Kim H, Chung HC, Rha SY, Noh SH, Jeung HC. Differential Prognostic Implications of Gastric Signet Ring Cell Carcinoma: Stage Adjusted Analysis From a Single High-volume Center in Asia. *Ann Surg* 2017; 265: 946-953 [PMID: 27232252 DOI: 10.1097/SLA.0000000000001793]

Gronnier C, Messager M, Robb WB, Thiobet T, Louis D, Luc G, Piessen G, Mariette C; FREGAT working group-FRENCH. Is the negative prognostic impact of signet ring cell histology maintained in early gastric adenocarcinoma? *Surgery* 2013; 154: 1093-1099 [PMID: 24075273 DOI: 10.1016/j.surg.2013.05.020]

Jiang CG, Wang ZN, Sun Z, Liu FN, Yu M, Xu HM. Clinicopathologic characteristics and prognosis of signet ring cell carcinoma of the stomach: results from a Chinese mono-institutional study. *J Surg Oncol* 2011; 103: 700-703 [PMID: 21306865 DOI: 10.1002/jso.21878]

Li C, Kim S, Lai JF, Hyung WJ, Choi WH, Choi SH, Noh SH. Advanced gastric carcinoma with signet ring cell histology. *Oncology* 2007; 72: 64-68 [PMID: 18004078 DOI: 10.1159/000111096]

Zu H, Wang H, Li C, Xue Y. Clinicopathologic characteristics and prognostic value of various histological types in advanced gastric cancer. *Int J Clin Exp Pathol* 2014; 7: 5692-5700 [PMID: 25373210]

Heger U, Blank S, Wiecha C, Langer R, Weichert W, Lordick F, Bruckner T, Dobrizz M, Burian M, Springer FD, Grenacher L, Siewert JR, Büchler M, Ott K. Is preoperative chemotherapy followed by surgery the appropriate treatment
for signet ring cell containing adenocarcinomas of the esophagogastric junction and stomach? Ann Surg Oncol 2014; 21: 1739-1748 [PMID: 24419755 DOI: 10.1245/s10434-013-3462-z]

59. Piessen G, Messager M, Robb WB, Bommetain F, Mariette C. Gastric signet ring cell carcinoma: how to investigate its impact on survival. J Clin Oncol 2013; 31: 2059-2060 [PMID: 23610107 DOI: 10.1200/JCO.2012.47.4338]

60. Lin SJ, Gagnon-Bartsch JA, Tan IB, Earle S, Ruff L, Pettinger K, Ylstra B, van Grienden N, Rha SY, Chung HC, Lee JS, Cheong JH, Noh SH, Aoyama T, Miyagi Y, Tsuburaya A, Yoshikawa T, Ajani JA, Bousioutas A, Yeho KG, Yong WP, So J, Lee J, Kang WK, Kim S, Kameda Y, Arai T, Zia Hausen A, Speed TP, Grabsch HI, Tan P. Signatures of tumour immunity distinguishing Asian and non-Asian gastric adenocarcinomas. Gut 2015; 64: 1721-1731 [PMID: 25385008 DOI: 10.1136/gutjnl-2014-308252]

61. Pernet S, Voron T, Perkins G, Lagorce-Pages C, Berger A, Taieb J. Signet-ring cell carcinoma of the stomach: Impact on prognosis and specific therapeutic challenge. World J Gastroenterol 2015; 21: 11428-11438 [PMID: 26523107 DOI: 10.3748/wjg.v21.i40.11428]

62. van der Post RS, Vogelaar IP, Carneiro F, Guilford P, Huntsman D, Hoogerbrugge N, Caldas C, Schreiber KE, Hardwick RH, Ausems MG, Bardram L, Benusiglio PR, Bisseling TM, Blair V, Bleiker E, Bousioutas A, Cats A, Coit D, DeGregorio L, Figueiredo J, Ford JM, Heijkoop E, Herrmann K, Lordick F, Wieder H, Weber WA, Becker K, Dobritz M, Fink U, Ulm K, Schuster T, Herrmann K, Lordick F, Wieder H, Weber WA, Becker K, Link T, Siewert JR, Schwaiger M, Fink U. FDG PET imaging of locally advanced gastric carcinomas: correlation with endoscopic and histopathological findings. Eur J Nucl Med Mol Imaging 2003; 30: 288-295 [PMID: 12552348 DOI: 10.1007/s00259-002-1029-5]

63. Ott K, Herrmann K, Lordick F, Wieder H, Weber WA, Becker K, Buck AK, Dobritz M, Fink U, Ulm K, Schuster T, Schwaiger M, Siewert JR, Krause BJ. Early metabolic response evaluation by fluorine-18 fluorodeoxyglucose positron emission tomography allows in vivo testing of chemosensitivity in gastric cancer: long-term results of a prospective study. Clin Cancer Res 2008; 14: 2012-2018 [PMID: 18381939 DOI: 10.1158/1078-0432.CCR-07-0953]

64. Chen J, Cheong JH, Yun MJ, Kim J, Lim JS, Hyung WJ, Noh SH. Improvement in preoperative staging of gastric cancer with positron emission tomography. Cancer 2005; 103: 2383-2390 [PMID: 15856477 DOI: 10.1002/cncr.21074]

65. Dassen AE, Lips DJ, Hoekstra CJ, Pruijt JF, Bosscha KA. FDG-PET has no definite role in preoperative imaging in gastric cancer. Eur J Surg Oncol 2009; 35: 449-455 [PMID: 19147324 DOI: 10.1016/j.ejso.2008.11.010]

66. Stahl A, Ott K, Weber WA, Becker K, Link T, Siewert JR, Schwaiger M, Fink U. FDG PET imaging of locally advanced gastric carcinomas: correlation with endoscopic and histopathological findings. Eur J Nucl Med Mol Imaging 2003; 30: 288-295 [PMID: 12552348 DOI: 10.1007/s00259-002-1029-5]

67. Ott K, Herrmann K, Lordick F, Wieder H, Weber WA, Becker K, Buck AK, Dobritz M, Fink U, Ulm K, Schuster T, Schwaiger M, Siewert JR, Krause BJ. Early metabolic response evaluation by fluorine-18 fluorodeoxyglucose positron emission tomography allows in vivo testing of chemosensitivity in gastric cancer: long-term results of a prospective study. Clin Cancer Res 2008; 14: 2012-2018 [PMID: 18381939 DOI: 10.1158/1078-0432.CCR-07-0953]

68. Chen JH, Kim C, Cho A, Kim YM, Jang SJ, Kim BO, Park CH, Hyung WJ, Ahn JB, Noh SH, Yun M, Rha SY. The clinical implications of FDG-PET/CT differ according to histology in advanced gastric cancer. Gastric Cancer 2019; 22: 113-122 [PMID: 29948387 DOI: 10.1007/s10120-018-0847-5]

69. Pak KH, Yun M, Cheong JH, Hyung WJ, Choi SH, Noh SH. Clinical implication of FDG-PET in advanced gastric cancer with signet ring cell histology. J Surg Oncol 2011; 104: 566-570 [PMID: 21671462 DOI: 10.1002/jso.21997]

70. Smyth EC, Verheij M, Allum W, Cunningham D, Cervantes A, Arnold D; ESMO Guidelines Committee. Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2016; 27: v38-v49 [PMID: 27664260 DOI: 10.1093/annonc/mdw350]

71. NCCN. Clinical Practice Guidelines in Oncology (NCCN Guidelines®)Gastric CancerVersion 2.2022. [cited 11 January 2022]. Available from: https://www.nccn.org/
randomised phase 2/3 trial.

oesophageal junction adenocarcinoma (FLOT4-AIO): results from the phase 2 part of a multicentre, open-label, leucovorin versus epirubicin, cisplatin, and fluorouracil or capecitabine in patients with resectable gastric or gastro-

Jäger E, Mönig S, Tannapfel A. Histopathological regression after neoadjuvant docetaxel, oxaliplatin, fluorouracil, and

W, Mahlberg R, Clemens M, Illerhaus G, Zirlik K, Behringer DM, Schmiegel W, Pohl M, Heike M, Ronellenfitsch U, Al-Batran SE

versus peri-operative chemotherapy for resectable gastric signet ring cell adenocarcinomas - PRODIGE 19 - FFCD1103 - C. Phase II/III multicentre randomised controlled trial evaluating a strategy of primary surgery and adjuvant chemotherapy

Piessen G

Upper Gastrointestinal Carcinomas: What is the Impact on Perioperative and Oncologic Outcomes?

Robb WB, Messager G, Le Malicot K, Robb WB, Di Fiore F, Guilbert M, Moreau M, Christophe V, Adenis A, Mariette C; FREGAT working group - FRENCH. The impact of perioperative chemotherapy on survival in patients with gastric signet ring cell adenocarcinoma: a multicenter comparative study. Ann Surg 2011; 254: 848-893; discussion 693 [PMID: 22050144 DOI: 10.1097/SLA.0b013e318235df67]

Lemoine N, Adenis A, Bouche O, Duhamel A, Heugue A, Leteurtre E, Amela E, Salleron J, Hebar M. Signet Ring Cells and Efficacy of First-line Chemotherapy in Advanced Gastric or Oesogastric Junction Adenocarcinoma. Anticancer Res 2016; 36: 5543-5549 [PMID: 27798928 DOI: 10.21873/anticancer.11138]

Charalampakis N, Nogueas Gonzalez GM, Elinova E, Wadhwa R, Shiozaki H, Shimodaira Y, Blum MA, Rogers JE, Harada K, Matamoros A Jr, Sagebiel T, Dan P, Minsky BD, Lee JH, Weston B, Bhutani MS, Estrella JS, Badgwell BD, Ajani JA. The Proportion of Signet Ring Cell Component in Patients with Localized Gastric Adenocarcinoma Correlates with the Degree of Response to Pre-Operative Chemoradiation. Oncology 2016; 90: 239-247 [PMID: 27046280 DOI: 10.1159/000443506]

Chen L, Shi Y, Yuan J, Wu Q, Han Y, Qin R, Jia B, Wei B, Wei L, Dai G, Jiao S. Evaluation of docetaxel- and oxaliplatin-based adjuvant chemotherapy in postgastrectomy gastric cancer patients reveals obvious survival benefits in docetaxel-treated mixed signet ring cell carcinoma patients. Med Oncol 2014; 31: 159 [PMID: 25119501 DOI: 10.1007/s12302-014-0159-5]

Lemoine N, Adenis A, Bouche O, Duhamel A, Heugue A, Leteurtre E, Amela E, Salleron J, Hebar M. Signet Ring Cells and Efficacy of First-line Chemotherapy in Advanced Gastric or Oesogastric Junction Adenocarcinoma. Anticancer Res 2016; 36: 5543-5549 [PMID: 27798928 DOI: 10.21873/anticancer.11138]

Messager M, Leefve JH, Pichot-Delahaye V, Souadka A, Piessen G, Mariette C; FREGAT working group - FRENCH. The impact of perioperative chemotherapy on survival in patients with gastric signet ring cell adenocarcinoma: a multicenter comparative study. Ann Surg 2011; 254: 848-893; discussion 693 [PMID: 22050144 DOI: 10.1097/SLA.0b013e318235df67]

Robb WB, Messager G, Gronnier C, Tessier W, Hee F, Piessen G, Mariette C; FREGAT (French EsoGastric Tumor) working group - FRENCH (Fédération de Recherche en Chirurgie). High-Grade Toxicity to Neoadjuvant Treatment for Upper Gastrointestinal Carcinomas: What is the Impact on Perioperative and Oncologic Outcomes? Ann Surg Oncol 2015; 22: 3632-3639 [PMID: 25676845 DOI: 10.1245/s10434-015-4423-5]

Piessen G, Messager M, Le Malicot K, Robb WB, Di Fiore F, Guilbert M, Moreau M, Christophe V, Adenis A, Mariette C. Phase II/III multicentre randomised controlled trial evaluating a strategy of primary surgery and adjuvant chemotherapy versus peri-operative chemotherapy for resectable gastric signet ring cell adenocarcinomas - PRODIGE 19 - FFCD1103 - ADC002. BMC Cancer 2013; 13: 281 DOI: 10.1186/1477-7817-13-281 [PMID: 23758655 DOI: 10.1056/NEJMoa055531]

Al-Batran SE, Hofheinz RD, Paullig K, Kopp HG, Haag GM, Luley KB, Meiler J, Homann N, Lorenzen S, Schmalenberg H, Probst S, Koenigsman M, Egger M, Prasnikar N, Caka C, Trojan J, Martens UM, Block A, Fischbach W, Mahlberg R, Clemens M, Illerhaus G, Zirlik K, Behringer DM, Schmiegel W, Pohl M, Heike M, Ronellenfitsch U, Schulz M, Bechstein WO, Kösgrainer A, Gaier T, Schirachner P, Hozacek W, Reichart A, Goetzte TO, Sievert M, Jäger E, Mönig S, Tannapfel A. Histopathological regression after neoadjuvant docetaxel, oxaliplatin, fluorouracil, and leucovorin versus epirubicin, cisplatin, and fluorouracil or capecitabine in patients with resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4-AIO): results from the phase 2 part of a multicentre, open-label, randomised phase 2/3 trial. Lancet Oncol 2016; 17: 1697-1708 [PMID: 27776843 DOI: 10.1016/s1470-2045(16)30531-9]

Al-Batran SE. Docetaxel, oxaliplatin, and fluorouracil/Lecovorin (FLOT) for resectable esophagogastrectomy cancer:...
updated results from multicenter, randomized phase 3 FLOT4-AIO trial (German Gastric Group at AIO). ESMO congress Abstract, 2017: LBA27_PR

97 Homann N, Pauligk C, Luley K, Werner Kraus T, Bruch HP, Atmaka A, Noack F, Altmannsberger HM, Jäger E, Al-Batran SE. Pathological complete remission in patients with oesophagogastric cancer receiving preoperative 5-fluorouracil, oxaliplatin and docetaxel. *Int J Cancer* 2012; 130: 1706–1713 [PMID: 21618509 DOI: 10.1002/ijc.26180]

98 Schütz C, Kullmann F, Kunzmann V, Fuchs M, Geissler M, Veithling-Kaiser U, Stauder H, Wein A, Al-Batran SE, Kubin T, Schäfer C, Stintzing S, Giessen C, Modest DP, Ridwelski V, Heinemann V. NeoFLOT: Multicenter phase II study of perioperative chemotherapy in resectable adenocarcinoma of the gastroesophageal junction or gastric adenocarcinoma—Very good response predominantly in patients with intestinal type tumors. *Int J Cancer* 2015; 137: 678–685 [PMID: 25530271 DOI: 10.1002/ijc.29403]

99 Iwasaki Y, Sasaki M, Yamamoto S, Nakamura K, Sano T, Katai H, Tsujinaka T, Nashimoto A, Fukushima N, Tsunaburya A; Gastric Cancer Surgical Study Group of Japan. Phase II study of preoperative chemotherapy with S-1 and cisplatin followed by gastrectomy for clinically resectable type 4 and large type 3 gastric cancers (JCOG0107). *J Surg Oncol* 2013; 107: 741–745 [PMID: 23400787 DOI: 10.1002/jso.23301]

100 Kinoshita T, Sasaki M, Sano T, Kato H, Furukawa H, Tsunaburya A, Miyashiro I, Kaji M, Ninomiya M. Phase II trial of S-1 for neoadjuvant chemotherapy against scirrhous gastric cancer (JCOG 0002). *Gastric Cancer* 2009; 12: 37–42 [PMID: 19309930 DOI: 10.1016/s1012-08-0496-1]

101 Terashima M, Iwasaki Y, Mizusawa J, Katayama H, Nakamura K, Kato H, Yoshikawa T, Ito Y, Kaji M, Kimura Y, Hiroo M, Yamada M, Kurita A, Takagi M, Boku N, Sano T, Sasaki M; Stomach Cancer Study Group, Japan Clinical Oncology Group. Randomized phase III trial of gastrectomy with or without neoadjuvant S-1 plus cisplatin for type 4 or large type 3 gastric cancer, the short-term safety and surgical results: Japan Clinical Oncology Group Study (JCOG0501). *Gastric Cancer* 2019; 22: 1044-1052 [PMID: 30827001 DOI: 10.1002/ijc.2019-00941-2]

102 Iwasaki Y, Terashima M, Mizusawa J, Katayama H, Nakamura K, Kato H, Yoshikawa T, Ito S, Kaji M, Kimura Y, Hiroo M, Yamada M, Kurita A, Takagi M, Lee SW, Takagane A, Yabusaki H, Hihara J, Boku N, Sano T, Sasaki M. Gastrectomy with or without neoadjuvant S-1 plus cisplatin for type 4 or large type 3 gastric cancer (JCOG0601): an open-label, phase 3, randomized controlled trial. *Gastric Cancer* 2021; 24: 492–502 [PMID: 33203030 DOI: 10.1007/s10120-020-01136-7]

103 Sakuramoto S, Sasaki M, Yamaguchi T, Kinoshita T, Fujii M, Nashimoto A, Furukawa H, Nakajima T, Ohashi Y, Imamura H, Higashino Y, Yamamura Y, Kurita A, Ari K; ACTS-GC Group. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. *N Engl J Med* 2007; 357: 1810–1820 [PMID: 17978289 DOI: 10.1056/NEJMoa0702252]

104 Noh SH, Park SR, Yang HK, Chung HC, Chung JJ, Kim SW, Kim HH, Choi JJ, Kim HK, Yu W, Lee JJ, Shin DB, Ji J, Chen JS, Lim Y, Ha S, Bang YJ; CLASSIC trial investigators. Adjuvant capecitabine plus oxaliplatin for gastric cancer after gastrectomy (CLASSIC): 5-year follow-up of an open-label, randomised phase 3 trial. *Lancet Oncol* 2014; 15: 1389–1396 [PMID: 25439693 DOI: 10.1016/s1470-2045(14)70473-5]

105 Sasako M, Sakuramoto S, Kato H, Kinoshita T, Furukawa H, Yamaguchi T, Nashimoto A, Fuji M, Nakajima T, Ohashi Y, Ikeda Y. Five-year outcomes of a randomized phase III trial comparing adjuvant chemotherapy with S-1 versus surgery alone in stage II or III gastric cancer. *J Clin Oncol* 2011; 29: 4387-4393 [PMID: 22010012 DOI: 10.1200/JCO.2011.36.5905]

106 Macdonald JS, Smalley SR, Benedetti J, Hundsahl SA, Estes NC, Steenmenn STM, Haller DG, Ajani JA, Gunderson LL, Jessup JM, Martenson JA. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med* 2001; 345: 725–730 [PMID: 11547744 DOI: 10.1056/NEJMoa0110187]

107 Cats A, Jansen EPM, van Grieken NCT, Siksorska K, Lind P, Nordsmark M, Meershoek-Klein Kranenbarg E, Boot H, Groen AK; Swellegrenelk HAM, van Laarhoven HWM, Putter H, van Sandick JW, van Berge Henegouwen MI, Hartgrink HH, van Tinteren H, van de Velde CJH, Verheij M; CRITICS investigators. Chemotherapy versus chemoradiotherapy after surgery and preoperative chemotherapy for resectable gastric cancer (CRITICS): an international, open-label, randomised phase 3 trial. *Lancet Oncol* 2018; 19: 616–628 [PMID: 29650363 DOI: 10.1016/S1470-2045(18)30132-3]

108 Park SH, Lim DH, Sohn TS, Lee J, Zang DY, Kim ST, Kang HJ, Oh SY, Hwang IG, Ji JJ, Shin DB, Yu JI, Kim KM, An JY, Choi MG, Lee JH, Kim S, Hong JY, Park JO, Park YS, Lim HY, Bae JM, Kang WK; ARTIST 2 investigators. A randomized phase III trial comparing adjuvant single-agent S-1, S-1 with oxaliplatin, and postoperative chemoradiation with S-1 and oxaliplatin in patients with node-positive gastric cancer after D2 resection: the ARTIST 2 trial*. *Ann Oncol* 2021; 32: 368–374 [PMID: 33278590 DOI: 10.1093/annonc/mdab011.2020.11.017]

109 Park SH, Sohn TS, Lee J, Lim DH, Hong ME, Kim KM, Sohn I, Jung SH, Choi MG, Lee JH, Bae JM, Kim ST, Park JO, Park YS, Lim HY, Kang WK. Phase III Trial to Compare Adjuvant Chemotherapy With Capecitabine and Cisplatin Versus Concurrent Chemoradiotherapy in Gastric Cancer: Final Report of the Adjuvant Chemoradiotherapy in Stomach Tumors Trial, Including Survival and Subset Analyses. *J Clin Oncol* 2015; 33: 3130–3136 [PMID: 25559811 DOI: 10.1200/JCO.2014.58.3930]

110 Dikken JL, van Sandick JW, Maurits Swellegrenelk HA, Lind PA, Putter H, Jansen EP, Boot H, van Grieken NC, van de Velde CJ, Verheij M, Cats A. Neo-adjuvant chemotherapy followed by surgery and chemotherapy or by surgery and chemoradiotherapy for patients with resectable gastric cancer (CRITICS). *BMC Cancer* 2011; 11: 329 [PMID: 21810227 DOI: 10.1186/1471-2407-11-329]

111 Stessin AM, Sisson C, Schwartz A, Ng J, Chao CK, Li B. Does adjuvant radiotherapy benefit patients with diffuse-type gastric cancer? *Cancer* 2014; 120: 3562–3568 [PMID: 25043858 DOI: 10.1002/cncr.28913]

112 Shechepkin IB, Evans SR, Chorny V, Osimsky S, Buras RR, Maligoven P, Shahabang M, Nauta RJ. Intensive preoperative radiotherapy with local hyperthermia for the treatment of gastric carcinoma. *Surg Oncol* 1994; 3: 37–44 [PMID: 8186689 DOI: 10.1096/jso.1994(9).0022-1]

113 Skoropad V, Berdov B, Zagrebin V. Concentrated preoperative radiotherapy for resectable gastric cancer: 20-years follow-up of a randomized trial. *Surg Oncol* 2002; 10: 72–78 [PMID: 12173383 DOI: 10.10200/jso.10102]

114 Skoropad VY, Berdov BA, Mardynsik VS, Titova LN. A prospective, randomized trial of pre-operative and
interoperative radiotherapy versus surgery alone in resectable gastric cancer. *Eur J Surg Oncol* 2000; 26: 773-779 [PMID: 11087644 DOI: 10.1053/ejso.2000.10022]

Ajan JA, Mansfield PF, Janjan N, Morris J, Pisters PW, Lynch PM, Feig B, Myerson R, Nivers R, Cohen DS, Gunderson LL. Multi-institutional trial of preoperative chemoradiotherapy in patients with potentially resectable gastric carcinoma. *J Clin Oncol* 2004; 22: 2774-2780 [PMID: 15254045 DOI: 10.1200/JCO.2004.01.015]

Ajan JA, Mansfield PF, Crane CH, Wu TT, Lunangonse S, Lynch PM, Janjan N, Feig B, Faust J, Yao JC, Nivers R, Morris J, Pisters PW. Paclitaxel-based chemoradiation in localized gastric carcinoma: degree of pathologic response and not clinical parameters dictated patient outcome. *J Clin Oncol* 2005; 23: 1237-1244 [PMID: 15718321 DOI: 10.1200/JCO.2005.01.305]

Ajan JA, Winter K, Okawara GS, Donohoue JH, Pisters PW, Crane CH, Greskovitch JF, Anne PR, Bradley JD, Willett C, Rich TA. Phase II trial of preoperative chemoradiation in patients with localized gastric adenocarcinoma (RTOG 9904): quality of combined modality therapy and pathologic response. *J Clin Oncol* 2006; 24: 3953-3958 [PMID: 16921048 DOI: 10.1200/JCO.2006.06.4840]

Alal AS, Zwalnen D, Bründer MA, de Peyer R, Morel P, Huber O, Roth AD. Neoadjuvant radiochemotherapy for locally advanced gastric cancer: long-term results of a phase I trial. *Int J Radiat Oncol Biol Phys* 2005; 63: 1286-1289 [PMID: 16137836 DOI: 10.1016/j.ijrobp.2005.05.033]

Wydmański J, Suwinski R, Poltoraš M, Maka B, Miszczyk L, Wolny E, Bielaczyc G, Zajusz A. The tolerance and efficacy of preoperative chemoradiotherapy followed by gastrectomy in operable gastric cancer, a phase II study. *Radiother Oncol* 2007; 82: 132-136 [PMID: 17287089 DOI: 10.1016/j.radonc.2007.01.009]

Leong T, Smithers BM, Michael M, Geskis V, Boussioutas A, Miller D, Simes J, Zalcberg J, Haustermans K, Lordick F, Schumacher C, Slawow C, Darling G, Wong R. TOPGEAR: a randomised phase III trial of perioperative ECF chemotherapy versus preoperative chemoradiation plus perioperative ECF chemotherapy for resectable gastric cancer (an international, intergroup trial of the AGITG/TROG/EORTC/NCIC CTG). *BMC Cancer* 2015; 15: 532 [PMID: 26914186 DOI: 10.1186/s12885-015-1929-x]

Slagter AE, Jansen EPM, van Laarhoven HWM, van Sandick JW, van Giessen NCT, Sikorska K, Cats A, Muller-Timmernann P, Hulshof MCCM, Boot H, Los M, Beerepoot LV, Peters FPJ, Hosapers GAP, van Etten B, Hartgrink HH, van Berge Henegouwen MI, Nieuwenhuijzen GAP, van Hillegersberg R, van der Peet DL, Grabsch HI, Verheij M. CRITICS-II: a multicentre randomised phase II trial of neo-adjuvant chemotherapy followed by surgery versus neo-adjuvant chemoradiotherapy and subsequent chemoradiotherapy followed by surgery in resectable gastric cancer. *BMC Cancer* 2018; 18: 877 [PMID: 30209910 DOI: 10.1186/s12885-018-4770-2]

Desiderio J, Chao J, Melstrom L, Warner S, Tozzi F, Fong Y, Parisi A, Woo Y. The 30-year experience-A meta-analysis of randomised and high-quality non-randomised studies of hyperthermic intraperitoneal chemotherapy in the treatment of gastric cancer. *Eur J Cancer* 2017; 79: 1-14 [PMID: 28480589 DOI: 10.1016/j.ejca.2017.03.030]

Coccolini F, Cotte E, Glihen O, Lotti M, Poiasina E, Catena F, Yonemura Y, Ansaloni L. Intraoperative chemotherapy in advanced gastric cancer. Meta-analysis of randomized trials. *Eur J Surg Oncol* 2014; 40: 12-26 [PMID: 24290371 DOI: 10.1016/j.ejso.2013.10.019]

Glihen O, Passot G, Villeneuve L, Vaudoyer D, Bin-Dorel S, Boscetti G, Piaton E, Garofolo A. GASTRICHIP: D2 resection and hyperthermic intraperitoneal chemotherapy in locally advanced gastric carcinoma: a randomized and multicenter phase III study. *BMC Cancer* 2014; 14: 183 [PMID: 24628950 DOI: 10.1186/1471-2407-14-183]

Götzte TO, Piso P, Lorenzen S, Bankstahl US, Pauligk C, Elshafei M, Amato G, Reind M, Bechstein WO, Königsrainer A, Mönig SP, Rau B, Schwarzbach M, Al-Batran SE. Preventive HIPEC in combination with perioperative FLOT versus FLOT alone for resectable diffuse type gastric and gastroesophageal junction type II adenocarcinoma - the phase III "PREVENT" - (FLOT9) trial of the AIO /CAOGI /ACO. *BMC Cancer* 2021; 21: 1158 [PMID: 34715810 DOI: 10.1186/s12885-021-08872-8]

Ishigami H, Tsuji Y, Shinohara H, Kodera Y, Kanda M, Yabusaki H, Ito S, Imano M, Yamashita H, Hidemura A, Yamaguchi H, Fukagawa T, Oba K, Kitayama J, Seto Y. Intraoperative Chemotherapy as Adjuvant or Perioperative Chemotherapy for Patients with Type 4 Scirrhous Gastric Cancer: PHOENIX-GC2 Trial. *J Clin Med* 2021; 10 [PMID: 34884367 DOI: 10.3390/jcm10253666]

Sugarbaker PH, Yu W, Yonemura Y. Gastrectomy, peritoneectomy, and perioperative intraperitoneal chemotherapy: the evolution of treatment strategies for advanced gastric cancer. *Semin Surg Oncol* 2003; 21: 233-248 [PMID: 14468781 DOI: 10.1002/nu.10042]

Sugarbaker PH. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in the management of gastrointestinal cancers with peritoneal metastases: Progress toward a new standard of care. *Cancer Treat Rev* 2016; 48: 42-49 [PMID: 27347669 DOI: 10.1016/j.ctrv.2016.06.007]

Al-Batran SE, Goetze TO, Drubay V, Vogel A, Winkler M, Lorenzen S, Novotny A, Pauligk C, Homann N, Jungbluth T, Reissfelder C, Caca K, Retter S, Horndasch E, Gumpp J, Bolling C, Fuchs KH, Blau W, Padberg W, Pohl M, Wunsch A, Michel P, Mannes F, Schwarzbach M, Schmelenbach H, Hofhaus M, Scholz C, Benckert C, Knorrenschild JR, Kannugieter V, Zander T, Alakus H, Hofheinz RD, Roedel C, Shah MA, Sasaki M, Lorenz D, Izibicki J, Bechstein WO, Lang H, Moeng SP. The RENAISSANCE (AIO-FLOTS) trial: effect of chemotherapy alone vs. chemotherapy followed by surgical resection on survival and quality of life in patients with limited-metastatic adenocarcinoma of the stomach or esophagogastric junction - a phase III trial of the German AIO/CAO-V/CAOGI. *BMC Cancer* 2017; 17: 893 [PMID: 29282088 DOI: 10.1186/s12885-017-3918-9]

NHI. Surgical Resection Plus Chemotherapy Versus Chemotherapy Alone in Oligometastatic Stage IV Gastric Cancer (SURIGASTAST). Report No.: NCT03042169, [cited 11 January 2022]. Available from: https://clinicaltrials.gov/ct2/show/NCT03042169

Koemans WJ, van der Kaaij RT, Boot H, Buffart T, Veenhof AAFA, Hartemink KJ, Grootsholten C, Snaeboijmonnson P, Retel VP, van Tinteren H, Vanhouvin S, van der Noort V, Houwink A, Hahn C, Huitema ADR, Lahaye M, Los M, van den Belselar P, Imhof O, Aalbers A, van Dam GM, van Etten B, Wijnhoven BPL, Luyer MDP, Boerma D, van Sandick
Drubay V et al. PCC gastric carcinoma review

JW. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy versus palliative systemic chemotherapy in stomach cancer patients with peritoneal dissemination, the study protocol of a multicentre randomised controlled trial (PERISCOPE II). BMC Cancer 2019; 19: 420 [PMID: 31065544 DOI: 10.1186/s12885-019-5640-2]

132 Glehen O, Gilly FN, Arvieux C, Cotte E, Boutitie F, Mansvelt B, Bereder JM, Lorimier G, Quenet F, Elias D; Association Française de Chirurgie. Peritoneal carcinomatosis from gastric cancer: a multi-institutional study of 159 patients treated by cytoreductive surgery combined with perioperatve intraperitoneal chemotherapy. Ann Surg Oncol 2017; 14: 2370-2377 [PMID: 28336386 DOI: 10.1245/s10434-016-1039-7]

133 Yang JX, Huang CQ, Suo T, Mei LJ, Yang GL, Cheng FL, Zhou YF, Xiong B, Yonenura Y, Li Y. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy improves survival of patients with peritoneal carcinomatosis from gastric cancer: final results of a phase III randomized clinical trial. Ann Surg Oncol 2011; 18: 1575-1581 [PMID: 21431408 DOI: 10.1245/s10434-011-1631-5]

134 Chia CS, You B, Decullier E, Vaudoyer D, Lorimier G, Abboud K, Bereder JM, Arvieux C, Boschetti G, Glehen O; BIG RENAPE Group. Patients with Peritoneal Carcinomatosis from Gastric Cancer Treated with Cytoreductive Surgery and Hyperthermic Intrapertitoneal Chemotherapy: Is Cure a Possibility? Ann Surg Oncol 2016; 23: 1971-1979 [PMID: 26573571 DOI: 10.1245/s10434-015-5081-3]

135 Bonnot PE, Piessen G, Pocard M, Meunier B, Bereder JM, Abboud K, Marchal F, Quenet F, Goede D, Miska S, Arvieux C, Pirro N, Wernert R, Rat P, Pezet D, Lefèvre J, Courvoisier T, Kiannanesh R, Meeus P, Glehen O. CYTO-CHIP: Cytoreductive surgery vs cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for gastric cancer with peritoneal metastasis: A propensity-score analysis from BIG RENAPE and FREGAT working groups. JCO 2018; 36: 8-8 [DOI: 10.1200/JCO.2018.36.4_suppl.8]

136 Bonnot PE, Lentinis A, Mercier F, Benzerdjeb N, Passot G, Pocard M, Meunier B, Bereder JM, Abboud K, Marchal F, Quenet F, Goede D, Miska S, Arvieux C, Pirro N, Wernert R, Rat P, Gagnière J, Lefèvre JH, Courvoisier T, Kiannanesh R, Vaudoyer D, Rosiere M, Meeus P, Villeneuve L, Piessen G, Glehen O; FREGAT and BIG-RENAPE Networks. Propensity of poorly cohesive gastric cancer after complete cytoreductive surgery with or without hyperthermic intraperitoneal chemotherapy (CYTO-CHIP study). Br J Surg 2021; 108: 1225-1235 [PMID: 34498666 DOI: 10.1093/bjsij/zhab200]

137 Königsrainer I, Horvath P, Struller F, Königsrainer A, Beckert S. Initial clinical experience with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in signet-ring cell gastric cancer with peritoneal metastases. J Gastric Cancer 2014; 14: 117-122 [PMID: 25061539 DOI: 10.5230/jgc.2014.14.2.117]

138 Huh CW, Jung DH, Kim JH, Lee YC, Kim H, Yoon SO, Yoon YH, Park H, Lee SI, Choi SH, Cheong JH, Noh SH. Signet ring cell mixed histology may show more aggressive behavior than other histologies in early gastric cancer. J Surg Oncol 2013; 107: 124-129 [PMID: 22991272 DOI: 10.1002/jso.23261]

139 Rouquier P, Ducroex M, Mahjoubi M, Pignon JP, Belféqih S, Oliveira J, Bognel C, Lasser P, Ychou M, Elias D. Efficacy of combined 5-fluorouracil and cisplatinum in advanced gastric carcinomas. A phase II trial with prognostic factor analysis. Eur J Cancer 1994; 30A: 1263-1269 [PMID: 7999410 DOI: 10.1016/0959-8409(94)90170-8]

140 Ajani JA, Rodriguez W, Bodoky G, Moiseyenko V, Lichinitser M, Gorbunova V, Vyvnychenko I, Garin A, Lang I, Falcon S. Multicenter phase III comparison of cisplatin/S-1 with cisplatin/infusional fluorouracil in advanced gastric or gastroesophageal adeno carcinoma study: the FLAGS trial. J Clin Oncol 2010; 28: 1547-1553 [PMID: 20159816 DOI: 10.1200/JCO.2009.25.4706]

141 Ajani JA, Abramov M, Bondarenko I, Shpyrky Y, Gorbunova V, Hontsa A, Otchenash N, Alisina M, Lazarev S, Feliu J, Elna A, Esko V, Balak K, Verma U, Benedetti F, Aoyama T, Mizuguchi H, Makris L, Rossi G; DIGEST Study Group. A phase III trial comparing oral S-1 based chemotherapy and intravenous cisplatin/docetaxel with cisplatin with untreated diffuse gastric cancer. Ann Oncol 2017; 28: 2142-2148 [PMID: 28911901 DOI: 10.1093/annonc/mdx275]

142 Pernet S, Mitry E, Samalien E, Daihan L, Dalban C, Ychou M, Seitz JF, Turki H, Mazard T, Zaan N, Lapérie C, Vaillant JN, Landi B, Rouquier P, Taihec J. Biweekly docetaxel, fluorouracil, leucovorin, oxaliplatin (TEF) as first-line treatment for advanced gastric cancer and adenocarcinoma of the gastroesophageal junction: safety and efficacy in a multicenter cohort. Gastric Cancer 2014; 17: 341-347 [PMID: 23739764 DOI: 10.1007/s11045-013-0266-6]

143 Eveno C, Juvoin I, Pocard M. PIPAC Estok 01: Pressurized IntraPeritoneal Aerosol Chemotherapy with cisplatin and doxorubicin (PIPAC CD) in gastric peritoneal metastasis: a randomized and multicenter phase II study. Pleura Peritoneum 2018; 3: 20180116 [PMID: 30911659 DOI: 10.1515/pp-2018-0116]

144 Nadiradze G, Giger-Pabst U, Zieren J, Strumberg D, Solass W, Reymond MA. Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPC) with Low-Dose Cisplatin and Doxorubicin in Gastric Peritoneal Metastasis. J Gastrointest Surg 2016; 20: 367-373 [PMID: 26511950 DOI: 10.1007/s11605-015-2995-9]

145 Alyami M, Bonnot PE, Mercier F, Laplace N, Villeneuve L, Passot G, Bakrin N, Kepenekian V, Glehen O. Pressurized intraperitoneal aerosol chemotherapy (PIPC) for unresectable peritoneal metastasis from gastric cancer. Eur J Surg Oncol 2021; 47: 123-127 [PMID: 32351204 DOI: 10.1016/j.ejso.2020.05.021]

146 Van Cutsem E, Bang YJ, Feng-Yi F, Xu JMM, Lee KW, Jiao SC, Chong JL, Lopez-Sanchez RL, Price T, Gladkov O, Stoss O, Hill J, Ng V, Lehle M, Thomas M, Kiemmaier A, Ruschoff J. HER2 screening data from ToGA: targeting HER2 in gastric and gastroesophageal junction cancer. Gastric Cancer 2015; 18: 476-484 [PMID: 25038874 DOI: 10.1007/s12020-014-0402-y]

147 Tanner M, Hollmén M, Junttila TT, Kapanen AI, Tommola S, Soini Y, Helin H, Salo J, Joensuu H, Silvo E, Elenius K, Isola J. Amplification of HER-2 in gastric carcinoma: association with Topoisomerase I/IIalpha gene amplification, intestinal type, poor prognosis and sensitivity to trastuzumab. Ann Surg Oncol 2016; 15: 273-278 [PMID: 15668283 DOI: 10.1093/annonc/mdo064]

148 Kim KC, Koh YW, Chang HM, Kim TH, Yoek JH, Kim BS, Jang SJ, Park YS. Evaluation of HER2 protein expression in gastric tissue: comparative analysis of 1,414 cases of whole-tissue sections and 595 cases of tissue microarrays. Ann Surg Oncol 2011; 18: 2833-2840 [PMID: 21468783 DOI: 10.1245/s10434-011-1695-2]

149 Chua TC, Merrett ND. Clinicopathologic factors associated with HER2-positive gastric cancer and its impact on survival outcomes—a systematic review. Int J Cancer 2012; 130: 2845-2856 [PMID: 21780108 DOI: 10.1002/ijc.26292]
Druab V et al. PCC gastric carcinoma review
metastasis. 

Imamura T
10.1016/j.jviscsurg.2015.09.021 resection for early gastric cancer with signet ring cell histology.

Wang Z
gastric cancer.

Ha TK
Kunisaki C
clinicopathological comparison with the other histological types.

Theuer CP
e4052 [PMID:

Lu M
Digestive Diseases and Sciences

Park JM
Kunii Y, Teshima S, Yamada Y, Saito T, Kikuchi S, Yamauchi H. Signet ring cell carcinoma of the stomach. 

Yokota T
Oncology

Takaoka S, Hosoda K, Suzuki Y, Oyama T, Hada M, Kojima Y, Omata M. Deficiency of mismatch repair genes is less

Hirotsu Y
DOI:

cancer (GC) patients and correlation with molecular features. 

Kim DY
Park YK, Joo JK, Ryu SY, Kim YJ, Kim SK, Lee JH. Clinicopathological characteristics of signet ring cell carcinoma of the stomach. 

Kunisaki C

Hass HG, Smith U, Läger C, Schäffer M, Wellhäuser U, Heth T, Markmann HU, Nehls O, Dzenzinger C. Signet ring cell carcinoma of the stomach is significantly associated with poor prognosis and diffuse gastric cancer (Lauren's): single-center experience of 160 cases. Onkologie 2011; 34: 682-686 DOI: 10.1159/000345454

Lee HH
Song KY, Park CH, Jeon HM. Undifferentiated-type gastric adenocarcinoma: prognostic impact of three histological types. 

Kim JP
Kim SC, Yang HK. Prognostic significance of signet ring cell carcinoma of the stomach. Surg Oncol 1994; 3: 221-227 DOI: 7834113 DOI: 10.1016/0960-7404(94)90037-x

Otsuji E, Yamaguchi T, Sawai K, Takahashi T. Characterization of signet ring cell carcinoma of the stomach. 

Surg Oncol 1998; 67: 216-220 DOI: 9579367 DOI: 10.1002/sia.1096-9098(199804)67:4<216::aid-sjo2-3.0.co;2-b

Yokota T, Kunii Y, Teshima S, Yamada Y, Saito T, Kikuchi S, Yamauchi H. Signet ring cell carcinoma of the stomach: a clinicopathological comparison with the other histological types. 

Tohoku J Exp Med 1998; 186: 121-130 DOI: 10.1620/tjem.186.121

Kim DY
Park YK, Joo JK, Ryu SY, Kim YJ, Kim SK, Lee JH. Clinicopathological characteristics of signet ring cell carcinoma of the stomach. 

Anz J Surg 2004; 74: 1060-1064 DOI: 15574148 DOI: 10.1111/j.1445-1433.2004.02368.x

Park JM
Jang YJ, Kim JH, Park SS, Park SH, Kim SJ, Mok YJ, Kim CS. Gastric cancer histology: clinicopathologic characteristics and prognostic value. 

Surg Oncol 2008; 98: 520-525 DOI: 18802956 DOI: 10.1002/jso.21150

Chiu CT, Kuo CJ, Yeh TS, Hsu JT, Liu KH, Yeh CN, Hwang TL, Jan YY, Lin CJ. Early signet ring cell gastric cancer. 

Dis Dig Sci 2011; 56: 1749-1756 DOI: 2104129 DOI: 10.1002/dss.21487-8

Lu M, Yang Z, Feng Q, Yu M, Zhang Y, Mao C, Shen L, Tang J. The characteristics and prognostic value of signet ring cell histology in gastric cancer: A retrospective cohort study of 2199 consecutive patients. 

Medicine (Baltimore) 2016; 95: e4052 DOI: 27399088 DOI: 10.1097/md.0000000000004052

Theuer CP
Nastanski F, Brewster WR, Butler JA, Anton-Culver H. Signet ring cell histology is associated with unique clinical features but does not affect gastric cancer survival. 

Ann Surg Oncol 1999; 65: 915-921 DOI: 100515534

Kunisaki C, Shimada H, Nomura M, Matsuda G, Otsuka Y, Akiyama H. Therapeutic strategy for signet ring cell carcinoma of the stomach. 

Br J Surg 2004; 91: 1319-1324 DOI: 15376179 DOI: 10.1002/bjs.4637

Ha TK, An JY, Youn HK, Noh JH, Sohn TS, Kim S. Indication for endoscopic mucosal resection in early signet ring cell gastric cancer. 

Ann Surg Oncol 2008; 15: 508-513 DOI: 18071825 DOI: 10.1002/ajso.21476-9

Wang Z, Zhang X, Hu J, Zeng W, Zhou Z. Clinicopathological features and outcomes in patients undergoing radical resection for early gastric cancer with signet ring cell histology. 

J Visc Surg 2015; 152: 357-361 DOI: 26481069 DOI: 10.1016/j.jviscsurg.2015.09.021

Imamura T, Komatsu S, Ichikawa D, Kawaguchi T, Kosuga T, Okamoto K, Konishi H, Shiozaki A, Fujiwara H, Otsuji E. Early signet ring cell carcinoma of the stomach is related to favorable prognosis and low incidence of lymph node metastasis. 

J Surg Oncol 2016; 114: 607-612 DOI: 27562147 DOI: 10.1002/jso.24377
