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REVIEW

Signet-ring cell carcinoma of the stomach: Impact on prognosis and specific therapeutic challenge

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Abstract

While the incidence of gastric cancer has decreased worldwide in recent decades, the incidence of signet-ring cell carcinoma (SRCC) is rising. SRCC has a specific epidemiology and oncogenesis and has two forms: early gastric cancer, which can be resected endoscopically in some cases and which has a better outcome than non-SRCC, and advanced gastric cancer, which is generally thought to have a worse prognosis and lower chemosensitivity than non-SRCC. However, the prognosis of SRCC and its chemosensitivity with specific regimens are still controversial as SRCC is not specifically identified in most studies and its poor prognosis may be due to its more advanced stage. It therefore remains unclear if a specific therapeutic strategy is justified, as the benefit of perioperative chemotherapy and the value of taxane-based chemotherapy are unclear. In this review we analyze recent data on the epidemiology, oncogenesis, prognosis and specific therapeutic strategies in both early and advanced SRCC of the stomach and in hereditary diffuse gastric cancer.

Key words: Gastric cancer; Signet ring cell carcinoma; Diffuse gastric cancer; Hereditary diffuse gastric cancer; CDH1

Core tip: Contrary to others gastric cancer, the incidence of signet-ring cell carcinoma (SRCC) of the stomach is rising worldwide. SRCC has a specific epidemiology and oncogenesis and has two forms: early gastric cancer, which can be resected endoscopically in some cases and which has a better outcome than non-SRCC, and advanced gastric cancer, which is generally thought to have a worse prognosis and lower chemosensitivity than non-SRCC. Its poor prognosis may be due at least in part to its more advanced stage. Therapeutic

strategies are emerging but still controversial, as the benefit of perioperative chemotherapy and the value of taxane-based chemotherapy.

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INTRODUCTION

Gastric cancer (GC) is a major public health problem, with 951000 new cases identified worldwide in 2012, representing 6.8% of all new cases of cancers. During 2012, 723000 patients died of a gastric cancer, accounting for 8.8% of deaths from cancer[1]. GC is the fifth most frequently diagnosed cancer and the third leading cause of cancer-related death in the world. Despite a decrease in the overall incidence of gastric cancer in recent decades, the incidence of signet-ring cell carcinoma (SRCC) is constantly increasing, in Asia, the United States and Europe, accounting for 35% to 45% of gastric adenocarcinoma cases in recent studies[2,3]. Its incidence increased 10-fold between 1970 and 2000[4].

HETEROGENEITY OF PATHOLOGICAL CLASSIFICATIONS

This increase in the proportion of SRCC in cases of gastric adenocarcinoma can be explained by changes in the pathological classifications used to characterize these cancers. Since the publication of the WHO classification of gastric cancers in 1990, signet-ring cell adenocarcinoma constitutes one specific histotype and therefore can be better identified among gastric cancers. Previously, signet-ring cell adenocarcinoma was classified as "diffuse type" according to Lauren's classification[5], "infiltrative type" by Ming[6], "undifferentiated type" by Nakamura[7] and "high grade" by the UICC[8].

Now, signet-ring cell carcinoma is defined according to the WHO's classification as a poorly cohesive carcinoma composed predominantly of tumor cells with prominent cytoplasmic mucin and a crescent-shaped nucleus eccentrically placed[9] (Figure 1A). It is important to understand that signet-ring cell adenocarcinomas are always classified, by definition, as "undifferentiated type" by Nakamura and as "diffuse type" by Lauren. But, conversely, not all gastric cancers classified as "undifferentiated" or "diffuse" are signet-ring cell cancers.

Also, although it is the usual histotype of linitis plastica, signet-ring cell adenocarcinoma should be distinguished from linitis plastica, which is defined macroscopically by thickening and rigidity of the gastric walls secondary to an abundant fibrous stromal reaction (Figure 1B). Thus 10% to 20% of cases of linitis plastica are not due to signet-ring cell adenocarcinoma[10].

EPIDEMIOLOGY OF SRCC:

Unlike non-SRCC, the incidence of SRCC of the stomach is rising

Since the advent of treatment to eradicate Helicobacter, the incidence of gastric adenocarcinoma has decreased. However, the incidence of SRCC is rising and SRCC is found in 8% to 30% of gastric cancers. SRCC epidemiology and risk factors differ substantially from those of other types of gastric adenocarcinoma. SRCC is more frequent in women than non-SRCC, with a sex ratio around 1, compared with less than 1/2 in gastric adenocarcinoma. SRCC occurs in younger patients, consistently 7 years before non-SRCC, with a mean age ranging from 55 to 61 years[3,11]. Ethnic distribution is unclear. A previous report showed a lower frequency in Asians, but SRCC as a disease entity was not clearly separated[9]. In a recent study in more than 10000 patients with gastric cancer, SRCC was significantly more common among black, Asian/Pacific Islander, American Indian/Alaska Native, and Hispanic ethnic groups[3]. In particular, in the Asian population, which represented 14% of the total population in this study, which is quite low considering the known epidemiology of gastric cancer in Asians, SRCC was found in more than 30% of patients. Another study on 1884 patients with less than 10% of Asian patients gave the same results[12]. But these studies were conducted in the United States and Canada and Asian patients living in North America may not be representative of the global Asian population. However, in recent large study in Asian countries SRCC was found in 15% of patients in South Korea[11], in 10% of Japanese patients[13] and in 6% to 15% of patients in China[14,15], although recent studies from the United States or European countries show a frequency of 25% to 30%[3,10].

SRCC has a distinct clinical presentation from non-SRCC

Considering clinical presentation, SRCC is more frequent in the middle stomach than non-SRCC. SRCC type is associated with more advanced cancer and is most frequent in stage 4, T3/T4 and N2 cancers. Paradoxically, SRCC is more frequent in early gastric cancer than in advanced gastric cancer in some reports[11]. In fact, SRCC in early gastric cancer and advanced gastric cancer may represent 2 distinct subsets with distinct implications. In advanced gastric cancer, peritoneal carcinomatosis is the most frequent metastatic site[16], and some authors recommend

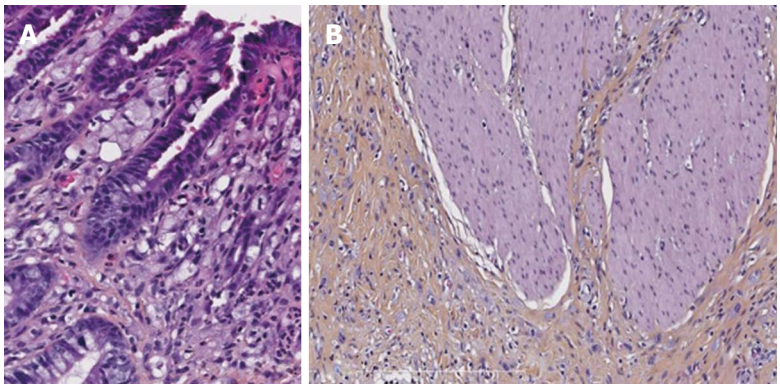

Figure 1 Focus of intramucosal signet ring cell carcinoma invading the lamina propria (T1a) (A) and signet ring cell carcinoma invading muscularis propria as single tumor cells with marked desmoplasia (B).

routine laparoscopic evaluation before treatment.

SRCC shares no risk factors with non-SRCC

In accordance with the different epidemiologies, SRCC could have different risk factors from non-SRCC. While non-SRCC is often multifactorial, infection with *Helicobacter pylori* (*H. pylori*) leading to chronic gastritis is involved in most cases of gastric cancer, with the exception of cardia cancer. However, the role of *H. pylori* in SRCC is more controversial. Indeed, since wide eradication of *H. pylori*, an *H. pylori*-negative gastric cancer (*H. pylori*NGC) entity has been emerging. This entity may include several subtypes, such as gastric adenocarcinoma of the fundic gland ((GA-FG-CCP) and SRCC, thus questioning the role of *H. pylori* in these histologic subtypes[17].

The role of other risk factors in gastric cancer (salt-preserved food, smoking, auto-immune gastritis) or cardia cancer (obesity…) is not well studied in SRCC.

SRCC is associated with specific germline mutations in the CDH1 gene, which encodes the epithelial cell adhesion protein E-cadherin in patients with hereditary diffuse gastric cancer

Early-onset diffuse gastric cancer (DGC), multi-generational DGC and lobular breast cancer clinically define hereditary diffuse gastric cancer (HDGC). Updated criteria were established by a multidisciplinary workshop in 2015[18].

CDH1 germline mutations are the main genetic cause of HDGC. The first CDH1 germline mutation was described in 1998, with a founder mutation identified in the New Zealand Maori population[19]. A heterozygous CDH1 germline mutation increases the lifetime of DGC and lobular breast cancer.

In the updated recommendations, compared with the 2010 guidelines[20], in the case of a familial history of gastric cancer the age of diagnosis is no longer required, as soon as DGC is confirmed histologically for at least one case. Two groups have been added in families in whom genetic testing can be considered: individuals with a personal or family history of cleft lip/cleft palate and DGC; *in situ* signet-ring cells and/or pagetoid spread of signet-ring cells in the stomach. The revised criteria are summarized in Table 1.

Using the 2010 criteria, the CDH1 detection rate is between 10% and 18% in countries with a low incidence. In contrast, this detection rate is much higher in the New Zealand Maori population[21-23]. A recent study updated penetrance data for CDH1 mutations carriers from 75 families. By the age of 80 years, the cumulative risk of DGC is estimated to be 70% for men (95%CI: 59%-80%) and 56% for women (95%CI: 44%-69%). Moreover, the cumulative risk of lobular breast cancer is reported to be 42% (95%CI: 23%-68%). No evidence for an increased risk of other types of cancer has been noted[21].

Within pathogenic CDH1 germline mutations, there is a majority of truncating mutations that do not lead to a functional protein. Rare large exonic deletions exist, with a frequency of about 5%[24]. As CDH1 is a tumor suppressor gene, a second somatic hit is needed for tumor initiation, which most frequently includes promoter methylation, and less frequently somatic mutation or loss of heterozygosity[25].

Other genes can be considered as candidates in HDGC predisposition: CTNN1A, BRCA2, PALB2 and MAP3K6. So far, no recommendation can be offered, due to lack of data[21,26].

CDH1 germline mutation carriers should be strongly advised to undergo prophylactic total gastrectomy, usually between 20 and 30 years old. Family history should be taken into account, especially the age of onset of clinical cancer in probands. Baseline endoscopy should be performed before surgery and *H. pylori* infection should be screened for and infected patients should be excluded. Gastrectomy examination and sampling should follow a specific protocol. Nearly all samples harbor signet-ring cells and many harbor T1a carcinoma[27].

Annual endoscopy should be offered to subjects who do not undergo surgery. To this end, a white light high-definition endoscope is recommended, for a least 30 min, with repeated inflation and deflation, in order

Table 1 Clinical hereditary diffuse gastric cancer testing criteria (from van der Post J Med Genet 2015[18])

Criteria include first and second degree relatives	
Established criteria	2 GC cases regardless of age, at least one confirmed DGC One case of DGC < 40 Personal or family history of DGC and LBC, one diagnosed < 50
Families in whom testing could be considered	Bilateral LBC or family history of 2 or more cases of LBC < 50 Personal or familial history of cleftlip/palate in a patient with DGC *In situ* signet ring cell and/or pagetoid spread of signet ring cells

GC: Gastric cancer; DGC: Diffuse gastric cancer; LBC: Lobular breast cancer.

to inspect the mucosa carefully. A minimum of 30 biopsies is recommended. Any endoscopically visible lesions are biopsied, including pale areas, but random sampling should also be performed, five biopsies being taken from each of the following anatomical zones: pre-pyloric area, antrum, transitional zone, body, fundus and cardia.

In women with a CDH1 mutation, breast surveillance includes annual breast magnetic resonance imaging (to which mammography can be added) starting at the age of 30, combined with an annual clinical breast examination. Prophylactic mastectomy is not recommended, but can be considered for some women.

There is no evidence to link CDH1 mutation to an increased risk of colorectal cancer, but case reports have mentioned colorectal and appendiceal SRCC in CDH1 mutation carriers. Therefore, in CDH1 mutation families in which colon cancer is reported in mutation carriers, colonoscopy screening can be proposed at age 40 or 10 years younger than the youngest diagnosis of colon cancer, whichever is younger, and repeated at intervals of 3-5 years[18].

SPECIFIC PATHWAYS ARE IMPLICATED IN SRCC CARCINOGENESIS

SRCC has a specific oncogenesis that differs from that of tubular gastric adenocarcinoma. The two main pathologic processes at a cellular level are loss of cell-cell adhesion molecules and accumulation of mucin in large vacuoles.

E-cadherin, which is encoded by the *CDH1* gene, is a cell-cell adhesion molecule and seems to play a key role in carcinogenesis. Its role in tumor progression and epithelial-mesenchymal transition has been widely studied in many types of cancer[28,29], but in SRCC E-cadherin may be involved earlier in tumor initiation[30]. E-cadherin deficiency has been reported to initiate carcinogenesis in a large proportion of SRCC cases, in both HDGC and sporadic SRCC. As seen above, germline inactivating truncating mutations in CDH1 are found in some, but not all, cases of HDGC[31]. These mutations confer an autosomal dominant susceptibility with variable penetrance according to the family. The carcinogenesis model in HDGC supposes that in patients carrying the germline mutation, a somatic event could occur in the second allele, such as a point mutation, loss of heterozygosity, or more frequently promoter hypermethylation[32]. Host-environment interaction could play a role in this somatic mutation (diet, gastritis, carcinogens)[30,31,33-35]. It is of note that CDH1 mutations are not found in familial intestinal gastric adenocarcinoma.

In sporadic SRCC, somatic mutations of CDH1 are also frequently involved compared with gastric adenocarcinoma, mostly promoter hypermethylation[36].

While CDH1 mutations seem to be the most frequent abnormality leading to SRCC, other adherence molecules could be involved in fewer cases, such as somatic mutations of β-catenin/APC genes or dysregulation of the Wnt/β-catenin pathway[37].

Moreover, expression of CDH1 and other adherence molecules could be downregulated upstream of various pathways. The phosphatidylinositol 3-kinase (PI3K) pathway may be involved in some cases of SRCC carcinogenesis. Briefly, the activated ErbB2/ErbB3 complex in SRCC binds PI3K leading to phosphorylation of tyrosine residues and activation of downstream pathways including p38 MAP kinase. Activation of p38 MAP kinase lead to loss of cell-cell contact by disruption of adherent junctions[38]. Moreover, the MEK1 pathway may complete the loss of cell-cell contact, and other pathways, as yet not well described, are probably involved. MUC4 has been reported to increase activation of the ErbB2/ErbB3 complex. MUC4 belongs to the family of mucins that are normally expressed in gastric mucosae (MUC1, MUC5AC, MUC6) or expressed *de novo* in gastric cancer (MUC2, MUC4). In SRCC, accumulation of mucins results in large vacuoles, which could therefore play a role in carcinogenesis. However, the mechanisms and pathways underlying mucin secretion and accumulation in cells are not well known.

Finally, a hormonal theory in which estrogen is involved in tumor initiation or progression or both has been developed to explain the increased incidence in women of SRCC compared with non-SRCC. Indeed, diffuse type gastric cancer is more likely to present estrogen receptors, even if this is not well established in the SRCC subtype[39-41]. However, while this mechanism has been suggested to be involved in the tumor process, there is no evidence that it plays a major role.

PROGNOSIS OF SIGNET-RING CELL GASTRIC ADENOCARCINOMA

While all studies agree on the poor prognosis of

Table 2 Studies assessing prognosis of the signet-ring cell histotype in early gastric cancers

Ref.	Number of patients in study	Number of early gastric cancers	SRCC frequency in early gastric cancer	Prognosis of SRCC (type of analysis)
Maehara *et al*[57] (1992)	1500	384	7.3%	Similar (univariate)
Otsuji *et al*[58] (1998)	1498	568	19.8%	Better (univariate)
Hyung *et al*[80] (2002)	3104	933	28.2%	Better (univariate)
Kim *et al*[45] (2004)	2358	561	16.7%	Similar (multivariate)
Kunisaki *et al*[43] (2004)	1113	513	23.4%	Better (multivariate)
Ha *et al*[42] (2008)	1520	1520	25.5%	Better (univariate)
Jiang *et al*[44] (2011)	2315	269	20.1%	Better (multivariate)
Kwon *et al*[11] (2014)	769	326	15.6%	Better (multivariate)
Gronnier *et al*[46] (2013)	421	421	25%	Similar (multivariate)

SRCC: Signet-ring cell carcinoma.

diffuse gastric adenocarcinoma according to Lauren's classification, including SRCC, the prognosis of signet-ring cell adenocarcinoma is still debated and appears to depend on the stage of the cancer at the time of diagnosis.

Prognosis of signet ring cell adenocarcinoma in early gastric cancers

For early gastric cancer, described by the Japanese Endoscopy Society as gastric cancer not extending beyond the submucosa whatever the lymph node status, the prognosis of SRCC has been reported in all studies as equivalent to or better than that of other gastric adenocarcinomas. Thus, in the largest published study of early gastric cancer in 1520 patients which compared prognosis of SRCC and non-SRCC, patients with SRCC had a better survival rate than patients with other gastric adenocarcinomas[42]. Among the nine studies that specifically studied the prognostic impact of the histotype (SRCC or non-SRCC) in early gastric cancers, five conducted a multivariate analysis to take account of potential confounding factors (Table 2). Three studies demonstrated that survival was better in early SRCC than in other early gastric cancers (Kunisaki *et al*[43] HR = 0.28; 95%CI: 0.08-0.91)[11,44] and two studies showed that the prognosis was similar[45,46].

This better overall survival observed in most studies could be related to the younger age at presentation for SRCC patients, as suggested by Gronnier *et al*[46]. Moreover, SRCC was more frequently limited to the mucosa and had fewer invaded lymph nodes than non-SRCC in early gastric cancer, which are two well-known prognostic factors for survival.

Prognosis of signet-ring cell adenocarcinoma in advanced gastric cancer

Conversely, in advanced gastric cancer, the prognosis of signet-ring cell adenocarcinoma is more controversial and is commonly thought to be poor. This was first suggested in retrospective studies[47-52], without distinction of SRCC among diffuse types. Two retrospective studies of more than 3500 patients with advanced SRCC showed a significantly worse 5-year survival rate than in non-SRCC[53,54] (Table 3). Other smaller studies showed a significant difference in overall survival between differentiated, SRCC and undifferentiated gastric cancer, SRCC being close to undifferentiated[11,14,55]. But other small studies did not indicate a significantly worse prognosis of SRCC[43-45,56-58]. Another study showed that SRCC was an independent predictor of poor prognosis in multivariate analysis[10], though this was not significant in another study with multivariate analysis[59]. Most of these studies were Asian.

Finally, the largest cohort comparing SRCC and non-SRCC, in more than 10000 patients, did not report that SRCC was a prognostic factor after adjustment for the tumor stage in advanced gastric cancer. However, Taghavi *et al*[3] did not specify the precise percentage of SRCC cases and did not use the WHO classification for more than 50% of SRCC cases. In this cohort, SRCC was not predictive of poor outcome, but was associated with more aggressive tumors. SRCC was more likely to be associated with an American Joint Committee on Cancer stage 4 tumor (50% *vs* 42%, $P < 0.001$), T3/T4 tumor (45.8% *vs* 33.3%, $P < 0.001$) and N2/N3 tumor (59.7% *vs* 51.8%). But in this large registry cohort, some confounding clinicopathological factors were not known, such as Performance Status, type of resection, and perioperative treatment. Moreover, it is quite surprising that patients with SRCC at a more advanced stage did not have a worse prognosis in univariate analysis. So, even though the size of the cohort is impressive, these data do not close the debate.

In conclusion, the prognosis of SRCC in advanced gastric cancer is controversial. Some reports suggest a worse prognosis, while others suggest that the presence of SRCC in gastric adenocarcinoma is not an independent predictor of prognosis after adjustment for the stage. But in most studies, SRCC was at a more advanced stage, suggesting a more aggressive SRCC phenotype and lower R0 resection rate[55], which could explain the poorer prognosis in some studies. This hypothesis is supported by results from several studies in which SRCC had a worse prognosis univariate analysis, but not in multivariate analysis, after adjustment for the tumor stage[14,45,54].

Table 3 Studies assessing the prognosis of the signet-ring cell histotype in advanced gastric cancer

Ref.	Number of patients in study	Number of advanced gastric cancers	SRCC frequency in advanced gastric cancer	Median 5-yr survival of SRCC (*vs* non-SRCC)	*P*-value
Maehera *et al*[57] (1992)	1500	1116	2%	48% (*vs* 33%)	NS
Kim *et al*[53] (1994)	3702	NP	NP	32% (*vs* 45%)	< 0.05
Otsuji *et al*[58] (1998)	1498	630	9.5%	44% (*vs* 28%)	NS
Yokota *et al*[56] (1998)	923	NP	NP	11% (*vs* 38%)	NS
Theuer *et al*[59] (1999)	3020	NP	NP	NP	NS (multivariate)
Kim *et al*[45] (2004)	2358	1797	6%	35% (*vs* 40%)	NS
Kunisaki *et al*[43] (2004)	1113	600	9%	NP	NS
Li *et al*[42] (2007)	4759	4759	14%	42% (*vs* 51%)	0.009
Messager *et al*[68] (2011)	159	NP	NP	9% (*vs* 24%)	0.038
Taghavi *et al*[3] (2013)	12246	6261	26.3%	NP	NS (multivariate)
Jiang *et al*[44] (2011)	2315	2046	7%	31.5% (*vs* 35.7%)	NS
Kwon *et al*[11] (2014)	769	443	12.8%	26% *vs* 50.5%[1]	0.004
Zu *et al*[14] (2014)	741	741	5.9%	43.4% *vs* 87.1%[2]	0.012[3]
Heger *et al*[55] (2014)	723	312	33.5%	NP	0.02 (multivariate)

[1]Ten-year survival; [2]*vs* well-differentiated cancer; [3]Comparison between all histotypes (well differentiated, moderately differentiated, poorly differentiated and SRCC). SRCC: Signet-ring cell carcinoma.

THERAPEUTIC STRATEGIES

Early gastric cancer: How far can we perform endoscopic resection?

The presence of lymph node metastases is considered as one of the most significant prognostic factors for overall and disease-free survival in patients with gastric cancer. Therefore, it is essential to highlight this potential lymph node involvement with appropriate surgery and consequently with extended lymphadenectomy, but also to propose postoperative chemotherapy when indicated.

However, for some early gastric cancers, the risk of lymph node metastasis is thought to be very low. Thus, patients with a well to moderately well differentiated tumor of less than 3 cm in size without submucosal invasion as well as patients with a well-differentiated, nonulcerated and limited submucosal lesion (T1sm1) of less than 3 cm in size have no risk of lymph node metastasis according to Gotoda *et al.* In these cases, endoscopic treatment including endoscopic mucosal resection or endoscopic submucosal dissection can be an alternative to radical surgery and has better perioperative outcomes and comparable long-term results[60,61].

Conversely, patients with early gastric cancer limited to the mucosa (clinically T1a), but with an ulcerated lesion, a lesion larger than 3 cm, with undifferentiated histotype or with lymphatic duct invasion have an increased risk of lymph node metastasis (detailed in Table 4). For these reasons, various guidelines have been established to define the indications for endoscopic resection. In Asia, endoscopic mucosal resections are limited to well or moderately differentiated tumors of less than 2 cm in size, limited to the mucosa and non-ulcerated, according to the Japan Gastric Cancer Association (JGCA) guidelines. Moreover, endoscopic submucosal resection, which enables more complete and extensive *en-bloc* resection, is indicated by JGCA guidelines for well-differentiated and non-ulcerated tumors of more than 2 cm in size and extending up to the submucosa (sm1) or for well-differentiated and ulcerated tumors of less than 3 cm limited to the mucosa or for undifferentiated and non-ulcerated tumors of less than 2 cm limited to the mucosa (Table 4).

In Europe and the United States, the EORTC St. Gallen International Expert Consensus defines the indications for endoscopic resections of early gastric cancer, largely following JGCA guidelines, except for gastric cancers with diffuse histology for which surgery is considered obligatory[62]. Thus, it is not recommended to perform endoscopic resection for early signet-ring cell gastric cancer in western countries, whatever the depth of invasion in the gastric walls. In Asia, SRCC limited to the mucosa, non-ulcerated and less than 2 cm in size can be resected by submucosal endoscopic resection[63]. In a recent study, Ha *et al*[42] supported this indication by demonstrating no lymph node metastasis in 77 patients with early gastric cancer confined to the mucosa, less than 2 cm in size and with no lymphatic involvement.

Resectable gastric cancers: Which procedure for signet-ring cell carcinoma?

For non-metastatic advanced gastric cancer, endoscopic resection is not possible due to a too high risk of lymph node metastases. Surgical resection is then essential to treat these tumors, combined with an adequate lymphadenectomy in order to assess the patient's prognosis, avoid stage migration and to propose the most appropriate therapeutic strategy.

The extent of this lymphadenectomy during gastrectomy for resectable advanced gastric cancer has been debated between Western and Asian surgeons for long time. Thus, despite a theoretical advantage of offering the widest lymphadenectomy possible, as advocated by Asian surgeons, two

Table 4 Incidence of lymph node metastasis in early gastric cancer (according with Gotoda *et al*[81])

Depth of invasion	Tumor size	Grade of differentiation	Ulcerated versus not ulcerated tumor	Incidence of LNM	Recommended treatment
Mucosal	< 2 cm	Well differentiated	Not ulcerated	0%	EMR
		Poorly differentiated	Not ulcerated	0%	ESD (Asia)/surgery (Western)
		Well differentiated	Ulcerated	0%	ESD
		Poorly differentiated	Ulcerated	2%	Surgery
	2-3 cm	Well differentiated	Not ulcerated	0%	ESD
		Poorly differentiated	Not ulcerated	1.7%	Surgery
		Well differentiated	Ulcerated	0%	ESD
		Poorly differentiated	Ulcerated	2.4%	Surgery
	> 4 cm	Well differentiated		1.7%	Surgery
		Poorly differentiated		7.3%	Surgery
Submucosal (sm1)	< 3 cm	Well differentiated		5.6%	ESD/Surgery
		Poorly differentiated		NC	Surgery
	> 3 cm	Well differentiated		2.6%	Surgery
		Poorly differentiated		6.5%	Surgery
Submucosal (sm2)	< 3 cm	Well differentiated		19%	Surgery
		Poorly differentiated		NC	Surgery
	> 3 cm	Well differentiated		27%	Surgery
		Poorly differentiated		NC	Surgery

ESD: Endoscopic submucosal dissection.

controlled randomized trials comparing D1 *vs* D2 lymph node dissection have demonstrated no 5-years survival benefit and higher postoperative mortality for D2 lymphadenectomy[64,65]. Nevertheless, both trials have received criticism over the relative inexperience of many different surgeons performing D2 lymphadenectomy, which could explain the higher mortality observed in D2 lymphadenectomy group. Furthermore after a follow-up of 15 years, D2 lymphadenectomy was associated with lower locoregional recurrence and gastric cancer-related death rates than D1 surgery in the Dutch D1D2 trial[66]. Thus, to deal with this lower locoregional recurrence rate associated with higher postoperative morbidity and mortality rates linked to splenectomy and distal pancreatectomy, a modified D2 lymphadenectomy (without splenectomy and distal pancreatectomy, named also D1,5 lymphadenectomy) was proposed, and become the standard lymphadenectomy for advanced gastric cancer in some European countries as in France, whereas the D2 lymphadenectomy remains the standard in others.

Despite a higher rate of lymph node involvement in SRCC, no specific recommendation is available about the type of lymphadenectomy to perform for advanced SRCC. As for other histological types, a modified D2 lymphadenectomy to remove at least 15 lymph nodes is recommended.

For distal gastric cancer, only two randomized clinical trials have investigated whether subtotal gastrectomy is sufficient compared with total gastrectomy. Both trials indicated no statistical difference in mortality or survival between the two surgical procedures. No subgroup analysis was conducted to evaluate these two procedures based on histological type. Thus, subtotal gastrectomy is recommended for antro-pyloric cancer, whatever the histological subtype. However, because the infiltrative nature of the SRCC results in more frequently invaded proximal and distal resection margins (20.3% *vs* 9.0% and 20.3% *vs* 4.0% in Piessen *et al*[10]), some authors routinely perform total gastrectomy combined with freezing of resection margins in the case of antro-pyloric SRCC.

Finally, due to a high rate of peritoneal carcinomatosis (17%) discovered during surgical resection of advanced SRCC, certain surgeons propose two specific therapeutic strategies for SRCC. First, staging laparoscopy can be performed routinely before any treatment to track any peritoneal carcinomatosis and therefore to modify treatment. Second, in the event of intraoperative discovery of resectable peritoneal carcinomatosis, palliative resection is not recommended for advanced SRCC because of an unacceptable three-fold higher risk of postoperative mortality for this histological subtype[67].

SRCC may have a different chemosensitivity profile than non-SRCC

SRCC is thought to be less chemosensitive than non-SRCC. However, no specific studies have assessed this hypothesis, which is supported by several controversial findings.

In a retrospective study of 924 cases of resected SRCC, comparing patients with and without peri-operative chemotherapy, the latter provided no benefit in terms of R0 resection rate (about 65%) or in survival[68]. Morever, perioperative chemotherapy was found to be an independent predictor of poor survival (HR = 1.4, 95%CI: 1.1-1.9, P = 0.042) and the authors suggested as an explanation that toxicity of neoadjuvant treatment was correlated with worse outcome[69]. However, this study suffers from several biases. The indication for perioperative treatment was

left to the investigator. Patients receiving perioperative chemotherapy had a more aggressive presentation than patients who received no perioperative treatment. Furthermore, the type of chemotherapy was left to the choice of the investigator. Perioperative standards are based on mostly non-SRCC or nonspecific studies and most patients receive 5FU + platinum component +/- epirubicin. Conversely, another large retrospective study in a perioperative setting suggested that SRCC has a lower response rate to neoadjuvant chemotherapy (mostly 5FU + platinum), but either the clinical or pathological response was significantly correlated with a better outcome[55]. This result highlights that perioperative treatment in SRCC may confer a theoretical benefit, but that the classic regimen seems insufficient.

SRCC could have a different chemosensitivity profile, and in particular recent data suggest that taxane-based therapy could be more efficient in SRCC. An ex vivo analysis of chemosensitivity of several human gastric cancer samples showed that SRCC and diffuse-type samples were significantly more sensitive to such drugs as mitomycin C, doxorubicin and docetaxel than intestinal-type samples, but not to 5FU or platinum[70], which is still most often used in the perioperative setting. In a comparison of docetaxel- and oxaliplatin-based chemotherapy in various SRCC histologies, Chen *et al*[71] found a benefit of docetaxel-based chemotherapy in mixed SRCC. However, the results were conflicting in pure SRCC in which there was no difference between the two types of chemotherapy. In a retrospective study with a limited number of patients (n = 17), docetaxel-based chemotherapy was associated with an 80% R0 resection rate and a median overall survival of more than 40 mo[72].

In a metastatic setting there are few data concerning chemosensitivity in specific subsets of SRCC in prospective trials. Twenty years ago Rougier *et al*[73] reported a 16% response rate in SRCC compared with 65% in non-SRCC. However, in a metastatic setting also, drugs such as taxanes may be more effective. We reported that in diffuse type SRCC and in SRCC patients treated with docetaxel, the combination of 5FU and oxaliplatin gave a response rate of more than 65% and seemed at least equivalent in non-SRCC[74,75].

Specific oncogenic pathways may induce specific sensitivity to targeted agents. There are no data concerning SRCC in recent trials testing targeted agents in gastric cancer. However, efficacy in diffuse type has been studied in a few trials. In the REGARDS trial, which was a phase Ⅲ trial testing ramucirumab, an anti-VEGFR2 antibody, versus best supportive care in pretreated patients with gastric cancer, ramucirumab provided a significant benefit in overall survival[76]. In subgroup analysis, a high benefit was found in the diffuse type (HR = 0.56; 95%CI: 0.36-0.85), but not in the intestinal type, suggesting higher sensitivity to antiangiogenics. This was not found in the RAINBOW trial testing ramucirumab in combination with paclitaxel[77], or with targeted therapy including anti-HER2, which is validated in HER2-overexpressing gastric cancer[78]. However, diffuse type was a small subgroup in these trials, and so we cannot draw conclusions regarding specific sensitivity.

Finally, immunotherapy should be tested in SRCC, as PDL1 is overexpressed in about 23% of cases of SRCC, and anti-PDL1 antibody is a promising treatment of GC[79].

In conclusion, whereas SRCC is thought to be less chemosensitive than non-SRCC, recent reports suggest it could have a specific sensitivity profile and be more sensitive to taxane-based chemotherapy or antiangiogenics. However, this has to be confirmed in a specific prospective trial. In a perioperative setting, the benefit of chemotherapy is controversial and a prospective randomized trial is under way to test this hypothesis. However, the chemotherapy regimen used is the old combination of epirubicin, cisplatin and fluorouracil, which may not be the optimal regimen in SRCC.

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