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REVIEW ARTICLE

Tailored treatment for signet ring cell gastric cancer

V. Mengardo[1] · E. Treppiedi[2] · M. Bencivenga[1] · Mariagiulia Dal Cero[1] · S. Giacopuzzi[1]

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Abstract
Gastric cancer with Laurèn diffuse types is increasing in the West. The raising trend is more evident when considering signet ring cells (SRC) histology. However, to control the biologic potential of this GC subtype, some hypotheses of tailored therapeutic strategies for SRC cancers have been made. A review of the literature was performed using the key words "signet ring cells" AND "gastric cancer". Results of literature review were descriptively reported. Endoscopic submucosal dissection (ESD), according to the Japanese extended criteria, could be a therapeutic option for early SRC tumours. However, according to the evidences from more recent studies, indications for ESD to these tumours types should be carefully considered. Concerning the optimal surgical treatment, considering the high lymphotropism and infiltrating behaviour of SRC histotype, the extension of gastric resection should be wider than for intestinal type cancer and laparoscopic surgery should be performed carefully. Moreover, D3 lymphadenectomy could provide a benefit in diffuse-type and SRC histology. The role of surgery in gastric cancer with peritoneal carcinomatosis is still debated and studies on this topic should stratify the good results according to GC histotype. Finally, despite the evidences of chemoresistance in SRC, ongoing randomized trials suggest that multimodal therapy could be the best treatment. Based on the assumption that SRC tumours have specific features, they deserve a specific multimodal treatment. However, a preliminary step to generate strong evidences in this field is the standardization of terminology used to define signet ring cells carcinoma.

Keywords Gastric cancer · Signet ring cell · Tailored treatment

Introduction

Gastric cancer (GC) is still one of the major causes of cancer-related death worldwide [1]. Recent epidemiological data show a changing in trends of GC histopathological subtypes. Specifically, a declining incidence of distal intestinal tumours has been reported, while the number of proximal intestinal cancers and Laurèn diffuse types is increasing. The raising trend is even more evident when considering tumours with signet ring cells (SRC) histology, according to the WHO classification [2–4].

SRCs tumours have an aggressive behaviour. Indeed, higher rate of peritoneal carcinomatosis, lymph node invasion and a lower rate of curative resections are reported for SRC compared to non-SRC tumours [5]. Despite these observations, the prognostic role of SRC histology is controversial [5, 6]. Some studies conclude that SRC type is an unfavourable prognostic factor [5], whereas other studies did not confirm this impact [6]. Other authors, when stratifying survival by tumour stage, report a paradoxical better survival in SRC compared to non-SRC tumours at early stages, suggesting that driver mutations controlling the metastatic potential of SRC may occur later in process of carcinogenesis [7, 8].

However, to control the biologic potential of this GC subtype, some hypotheses of tailored therapeutic strategies for SRC cancers have been made. The present overview aims to report the existing evidences supporting the need of dedicated treatment options for GC with SRC histology.

The article is part of topical collection on Gastric Cancer Surgery.

✉ V. Mengardo
valentina.mengardo@gmail.com

[1] General and Upper GI Surgery Division, University of Verona, Piazzale Aristide Stefani 1, 37126 Verona, Italy

[2] Department of Surgery-Division of General Surgery Fondazione Poliambulanza, Istituto Ospedaliero Brescia, Brescia, Italy

Materials and methods

A review of the literature was performed by searching in PubMed for papers using the key words "signet ring cells" and "gastric cancer". Only studies in English language focused on treatment of SRC gastric cancer were considered. Results of literature review were descriptively reported.

Evidences of tailored treatment in SRC

Endoscopic resection

According to the extended criteria proposed by Gotoda et al. [9], the endoscopic submucosal dissection (ESD) could be a possible therapeutic option also for some cases of early gastric cancer with undifferentiated histology including SRC tumours. However, although many retrospective studies from the East, showed good long-term results after curative endoscopic resection following extended criteria [10], many doubts persist regarding the safety of such therapeutic approach specifically in case of neoplasms with undifferentiated histotype [11].

Currently, there are no results of dedicated prospective studies. In addition, cases of lymph node metastasis have been reported in tumours with undifferentiated histotype that could be removed endoscopically according to the extended criteria. Chung et al. [12] in a surgical series of 1721 patients, reported 1.15% (3/261 patients) of lymph node metastasis in tumours with undifferentiated histotype, less than 2 cm with no ulceration. Moreover, Hirasawa et al. [13] reported a case of gastric adenocarcinoma with undifferentiated histotype radically removed by ESD confirming the conventional histology of 13-mm intramucosal lesion, without radiologically evident perigastric lesion ulceration, which was then positive for lymph node metastasis.

A further issue in generalizing the indications from Eastern studies to the West is the different pathological classification routinely used for gastric cancer. Indeed, in the above-mentioned studies [9, 10], proving the safety of endoscopic resection for early tumours according to expanded indications; the Japanese pathological classification of GC has been used. However, there is no perfect correspondence between the Laurèn [14] and WHO [15] classifications that are commonly adopted in the West and the Japanese classification [16]. Indeed, undifferentiated histotype of the Japanese classification comprises both the Laurèn diffuse, including WHO SRC tumours, and the poorly differentiated intestinal Laurèn types.

Of note, Western authors reported in early gastric cancer a rate of nodal metastasis ranging between 5 and 21% [17, 18] that is higher of those observed in Eastern series. This may due to differences in tumour biology, specifically to a different proportion of tumours with Laurèn diffuse and SRC histology. As such, possible indications for endoscopic resection to these tumours types should be carefully considered. This is also suggested by more recent data specifically focused on early gastric cancer with SRC histotype in which a higher rate of nodal involvement compared to other histotypes has been observed [19–26].

In conclusion, more studies are needed to assess the oncological safety of endoscopic resection for SRC tumours after a standardized histological definition between Eastern and Western studies.

Surgical treatment

The debate on optimal surgical treatment takes into account both the issue of resection margins and the extension of lymphadenectomy.

With regard the resection margins, Piessen et al. demonstrated that SRC tumours have lower R0 resection rate due to their infiltrating behaviour leading to more positive vertical margins despite more extensive surgery [5]. According to these evidences, the extension of gastric resection should be wider than for intestinal type cancer. If the Italian guidelines consider appropriate a proximal margin of 5 cm [27], the German's suggest even 8 cm as desired margin [28]. Additionally, laparoscopic surgery should be performed carefully in advanced gastric cancer with diffuse type as it is related to a higher rate of positive surgical margin compared to intestinal type tumours. Indeed, Kelly et al. showed a 10% of R1 resection after laparoscopy compared to 1% of open approach, among these R1, 75% were SRC tumours [29].

Another characteristic of diffuse tumours is the lymphotropism and the greater propensity to metastatize to third level nodes as compared to intestinal tumours [30]. Nowadays, according to Eastern and Western guidelines [11, 27, 28], the standard of care for locally advanced GC is D2 lymphadenectomy. But, some studies tried to evaluate if D3 lymphadenectomy could provide a benefit in subgroups of GC at high risk of nodal metastases, namely the tumours with diffuse-type and SRC histology. There is evidence that D3 lymphadenectomy is associated with a lower risk of locoregional recurrence in tumours with diffuse histology compared to D2 [31].

SRC tumours are also characterized by a higher prevalence of synchronous or metachronous peritoneal carcinomatosis. As reported by Kim et al. [32] unsuspected peritoneal carcinomatosis is significantly more frequent in SRC compared to non-SRC cases (18.6% vs. 6.0%, $p = 0.013$) leading to poorer prognosis. Based on these observations, some authors suggest to better evaluate the role of Hyperthermic intraperitoneal chemotherapy (HIPEC) in the

tailored treatment of SRC gastric tumours both in prophylactic and therapeutic settings. Desiderio et al. showed a better long-term survival rate, in locally advanced (cT3/4) tumours with negative cytology underwent to prophylactic HIPEC [33]. More debated is the therapeutic use of HIPEC. In patients with positive peritoneal cytology at diagnosis, when converted to a negative cytology by neoadjuvant chemotherapy, surgery does not improve survival [34]. But, Badgwell et al. documented an improved overall survival (median OS of 30.2 months) for patients with gastric cancer metastasis limited to the peritoneum who underwent multimodality treatment with chemotherapy and HIPEC repeated until obtaining negative cytology, and successively undergone to surgery [35]. Moreover, the role of surgery in gastric cancer with peritoneal carcinomatosis is still debated. In a recent Korean study, Kim analysed the results of conversion surgery in a series of patients with peritoneal seeding. They interestingly, found that the median survival time of patients underwent curative conversion surgery was 37 months, and the 3-year survival rate was 50%. The differences between the studied groups were statistically significant [36]. Studies on this topic should stratify the results according to GC histotype.

Multimodal therapy

Since 2005 when the results of the MAGIC study were published [37], perioperative chemotherapy (PCT) based on epirubicin–cisplatinum-5-fluorouracil (ECF) was recommended for locally advanced gastric cancer. However, there are some evidences of chemoresistance in SRC gastric tumours. Heger et al. analysed response and prognosis after neoadjuvant treatment in 723 locally advanced esophagogastric adenocarcinomas. They found that SRC carcinoma was associated with more aggressive behaviour and lower survival rate. However, although response to neoadjuvant chemotherapy is rare in SRC, it is associated with improved outcome [38].

Messager et al. showed that PCT does not provide any survival advantage in SRC due to an absence of both cytotoxic and cytostatic effects, in these cases delay in definitive surgery may favour tumour progression [39]. Piessen et al. in a randomised phase II/III trial hypothesise that a policy of primary surgery followed by adjuvant chemotherapy will improve overall survival compared to a standard perioperative chemotherapeutic strategy [40]; in this case, however, we have to face to the difficulty to accomplish an adjuvant therapy after a major surgery.

Preliminary data of Al Batran et al.'s phase III trial show promising results by the administration of FLOT scheme as perioperative chemotherapy in GC with a significantly increased proportion of patients achieving pathological complete regression compared with ECF/ECX [41]. This effect is especially evident in intestinal type tumours but Al Batran et al.'s preliminary data showed that also SRC tumours could have a good response. However, also in the field of multimodal treatment SRC needs special considerations in the choice of best therapeutic option.

Conclusions

Gastric cancer with SRC histology is increasing in the West [4]. Based on the assumption that SRC tumours have specific features, they deserve a specific multimodal treatment. The evidences reported in the present overview suggest that indications for endoscopic resection, the extent of surgery and the type of multimodal treatment should be tailored on the characteristics of SRC tumours. However, a preliminary step to generate strong evidences in this field is the standardization of terminology used to define signet ring cells carcinoma. Indeed, currently the terms "diffuse type" cancer, "Poorly Cohesive" and "Signet Ring Cell" gastric carcinomas, according to the Laurén classification and 2010 WHO classification, respectively, or also "linitis plastica" are used indiscriminately. This represents a hot topic of clinico-biological research in gastric cancer.

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Compliance with ethical standards

Conflict of interest The Authors declare that they have no conflict of interest.

Research involving human participants and/or animals The research does not involve human participants and/or animals.

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