Gastric signet ring cell carcinoma, does it confer a worse prognosis and treatment outcome?

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Abstract

Background and aim: Gastric cancer represents the fifth most common cancer worldwide and the fourth most common cause of cancer related death. In recent years many studies focused on the increased incidence of signet ring cell carcinoma (SRCC) which is considered a poorly cohesive carcinoma with poor prognosis, this study aims to define any significant difference in clinical presentation and survival between gastric SRCC and non-signet ring cell carcinoma (non-SRCC).

Patients and methods: This is a prospective cohort study which included 68 adenocarcinoma gastric cancer patients 42 with non-SRCC and 26 with SRCC, presented to Medical Oncology Department and Radiotherapy Department, South Egypt Cancer Institute (SECI), between January 2015 to December 2017, patients were followed up for 3 years . All patients performed complete laboratory and radiological investigations for accurate evaluation and staging. Data analysis was done by SPSS version 21, difference was considered statistically significant at P-value < 0.05. Survival curves were conducted by using the Kaplan-Meier methods and were compared with the log-rank test.

Results: There was no significant difference between non-SRCC and SRCC as the one year OS was 18% for non-SRCC and 17 % for SRC while the two year OS was 5% and 4% respectively, the median OS for non-SRCC was 7 months and for SRC was 7.5 months with p-value = 0.669. While one year PFS reached 30% in non-SRCC and 18% for SRC, and two year PFS was 11% for non-SRCC and 10% for SRC, the median PFS for non-SRCC reached 5 months and 5.5 months for SRC with p-value=0.494.

Conclusions: There was no significant difference between SRCC and non-SRCC in terms of OS and PFS.

Keywords: gastric SRCC, gastric non-SRCC, survival.

Introduction:

Gastric cancer represents the fifth most common cancer worldwide and the fourth most common cause of cancer related death showing a median overall survival of around 12 months for advanced stage [1]. Gastric cancer shows genetic and molecular variabilities leading to heterogenous disease presentations [2]. The average age for gastric cancer is more than 50 years of age and it is very rare in younger population as in patients of younger than 45 years of age being only 10 % of cases [3]. In recent years many studies focused on the increased incidence of SRCC subtype which may be attributed to new pathological classifications of cancer [4].

Signet ring cell carcinoma SRCC is rare adenocarcinoma subtype, which is found commonly in the stomach and occasionally in the breast, ovary, colon, rectum, and gallbladder. Gastric signet ring carcinoma is considered a poorly cohesive carcinoma. The signet ring carcinoma cell has a characteristic ring appearance which is attributed to the shape of the nucleus being crescent and the cytoplasm being mucin-rich [5]. The incidence of GC has declined due to Helicobacter pylori eradication treatments. However, the incidence of gastric SRCC has been rising in recent years. It accounts for approximately 15%–28% of GC, and this percentage is still increasing [4].

SRCC has two forms: early gastric cancer which can be resected endoscopically in selected cases and therefore can even show a better outcome than adenocarcinoma, while the other form is the advanced gastric cancer which is thought to have a worse prognosis and less chemosensitivity, however this fact is still showing controversial results, so this hypothesis should be properly assessed in specific studies [4].

Signet ring cells are characterized by their low expression of E-cadherin which is related to cell-to-cell adhesion. Low expression of E-cadherin is associated with cancer cell migration and invasion to adjacent cells [5].

There are several systems for histopathological classification of gastric carcinoma, the most popular classification systems known to pathologists and clinicians are Lauren, Japanese Gastric Cancer Association (JGCA) and World Health Organization (WHO) [6].

Lauren classification depends on microscopic features of the neoplastic cells, two main types of

adenocarcinoma of the stomach are encountered, namely the intestinal type and diffuse type, the latter included the signet ring cell carcinoma [7].

The WHO classification system issued in 2010 divided gastric adenocarcinoma into several types according to architectural pattern. The most common are tubular, papillary, mucinous and mixed adenocarcinoma. The poorly cohesive carcinoma includes the signet ring carcinoma diagnosed when more than 50% of the neoplastic growth exhibit signet ring cells with eccnteric nuclei [8].

The Cancer Genome Atlas (TCGA) Network divided the primary gastric cancers into: Epstein Barr virus (EBV) associated, microsatellite instability (MSI) associated, chromosomal instability associated and genomically stable. As regard to the histological subtype the signet ring cell carcinoma was included in genomically stable group [9].cancer genome atlas

Asian guidelines adopt submucosal endoscopic resection of early gastric SRCC in specific indications as the tumor being limited to the mucosa, non-ulcerated and less than 2 cm in size, but on the contrary western countries don't recommend submucosal endoscopic resection whatever the depth of invasion in the gastric walls [10].

The gastric lymphatic system is located deep in the mucosal layer raising concerns about potential lymphovascular invasion, lymph node metastasis, and remnant cancer after endoscopic resection, thus surgical resection remains the mainstay treatment for early stage gastric SCCR [11].

Two landmark trials, INT0116 1 and MAGIC, 2 established the role of postoperative chemoradiation (INT0116) and perioperative chemotherapy (MAGIC) in the treatment of resectable gastric cancer to become the standard treatment for resectable gastric cancer [12,13]. Subsequently, the CLASSIC trial 4 showed that, after a D2 resection, adjuvant chemotherapy improves disease-free survival [14].

The chemosensitivity of SRCC to specific protocols with the evaluation of the use of peri-operative therapy or taxane based chemotherapy needs to be identified [15].

Aim of the study

Evaluating SRCC pathological type as an independent prognostic factor affecting clinical presentation and treatment outcome for gastric adenocarcinoma.

Patients and methods

Study design

This is a prospective cohort study which included 68 adenocarcinoma gastric cancer patients presented to Medical Oncology Department and Radiotherapy Department, SECI, between January 2015 to December 2017, patients were followed up for 3 years. The study consists of two groups, the first consists of 42 patients with non-SRCC and the second of 26 with SRCC. The study was approved by SECI ethics committee and an informed written consent was taken from all patients.

Inclusion criteria

All patients 18 years and older presented with gastric adenocarcinoma including those with SRCC were enrolled in the study either at an early stage, advanced or metastatic stage.

Exclusion criteria

Patients with any other pathology other than gastric adenocarcinoma, patients who received any line of chemotherapy or chemoradiation before enrollment in the study were excluded. Patients with severe comorbid condition making modalities of treatment not feasible (chemotherapy, chemoradiation , surgery).

Pretreatment evaluation

All patients performed complete laboratory and radiological investigations for accurate evaluation and staging. Radiological evaluation included MSCT pelviabdomin and chest, PET/CT in some selected cases, contrast-enhanced CT examinations were performed by 16-channel multidetector CT scanner, the role of preoperative contrast enhanced CT scan was local staging to detect depth of invasion of the tumor, lymph node involvement and metastatic work-up (Figure 1 & Figure2).

Follow up CT was considered for monitoring response to treatment and post-treatment evaluation. In metastatic cases the sites and sizes of metastasis were recorded to be compared with follow up CT scans after receiving chemotherapy or chemoradiation.

Initial biopsies were taken by upper endoscopy, and patients eligible for surgery performed pre-operative diagnostic laparoscopy. Postoperative specimens were properly evaluated for pathological staging as T, N, and safety margins.

Histopathologic evaluation

All specimens either preoperative endoscopic biopsy or post-operative gastrectomy specimens were sent to pathology laboratory at SECI in 10% formalin, processed as usual and the hematoxylin & eosin (Hx&E) slides examined separately by two experienced pathologists (Figure 3).

SRCC was diagnosed when more than 50% of tumor cells exhibiting signet ring features with eccentric nuclei according to WHO 2010. TNM staging were also detected according to WHO 2010.

The lymphovascular invasion and perineural invasion when suspected CD34 & S100 were done respectively for confirmation (Figure 4).

Treatment protocol

26 patients received adjuvant chemoradiotherapy (Intergroup 0116) protocol, 14 with non-SRCC and 12 with SRCC as a twenty one day cycle of oral capecitabine 1000 mg/m^2 twice daily for 14 days followed by chemoradiation with 825 mg/m2 capecitabine twice daily five days weekly for five weeks, one week after completion of radiotherapy two more cycles of capecitabine were given [16].

32 patients with metastatic disease, 22 with non-SRCC and 10 with SRCC received palliative CAPEOX (capecitabine/oxaliplatin) protocol as a twenty one day cycle of oral capecitabine 1000 mg/m^2 twice daily for fourteen days and oxaliplatin 130 mg/m^2 infusion on day one [17].
10 patients with unresectable tumors received capecitabine following radical chemoradiation.

Radiotherapy technique

36 patients received chemoradiotherapy 26 as post-operative and 10 as radical in unresectable tumors, 20 patients with non SRCC and 16 with SRCC, radiotherapy delivered was 4500 -5040 c Gy in 25-28 fractions within 5 weeks using 6 and 15 MV photons delivered concurrently with Capecitabine 825mg/m^2 every 12 hours, five days per week during radiotherapy.

In radical chemoradiation the gross tumour volume (GTV) for primary tumor and lymph nodes was identified as seen on CT, and endoscopic evaluation. The clinical target volume (CTV) was defined as the gross tumour volume plus a 5-cm margin superior and inferior and 2-cm margin radial to the tumour including the entire stomach, all tumour extensions and draining lymph nodes (perigastric, celiac, porta-hepatis, gastroduodenal, splenic, hilar, suprapancreatic, pancreatoduodenal, paraaortic, and, paraoesophageal).

Coverage of nodal areas was modified according to the clinical circumstantances and risk of toxicity. In post-operative chemoradiation the clinical target volume (CTV) included the initial tumor bed, remaining stomach, anastomotic site and regional lymph nodes.

Statistical analysis

Data analysis was done by SPSS version 21(IBM Inc., USA). Data was described as frequencies (percentages) and the differences between variables were analyzed by chi-square test. OS and PFS were estimated using Kaplan-Meier method. Differences between survivals of different groups were done by Log rank (Mantel- Cox) test. Probability (p-value) was considered significant if equal to or less than 0.05 [18].

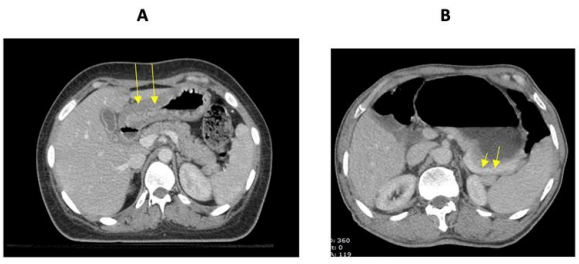

Figure 1: CT scans of two patients with SRCC
(A) 26-year-old female with SRCC, contrast-enhanced CT scan shows diffuse gastric wall thickening with more than 50% preservation of the thin high-attenuating inner layer (long arrows).
(B) 50 year old male with SRCC, contrast-enhanced CT scan shows enhancing focal gastric wall thickening (short arrows) at greater curvature of stomach. The attenuation of the enhancing thickened gastric wall is higher than that of the liver

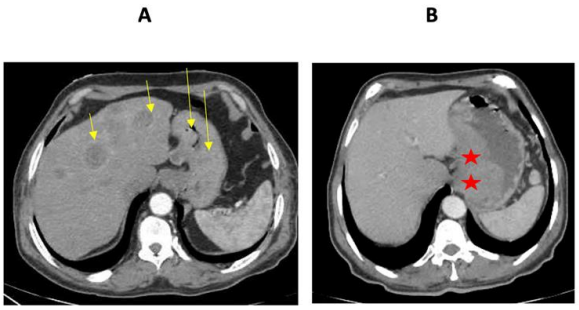

Figure 2: CT scans of two patients with Non-SRCC
(A) 68 year old male with Non-SRSC, contrast-enhanced CT scan shows diffuse gastric thickening (long arrows) with multiple small hepatic focal lesions (short arrows).
(B) 55 years old male with Non-SRSC, contrast-enhanced CT scan shows a huge mildly enhanced polypoidal soft tissue mass lesion seen at occupied most of the lessar curvature of the stomach (stars).

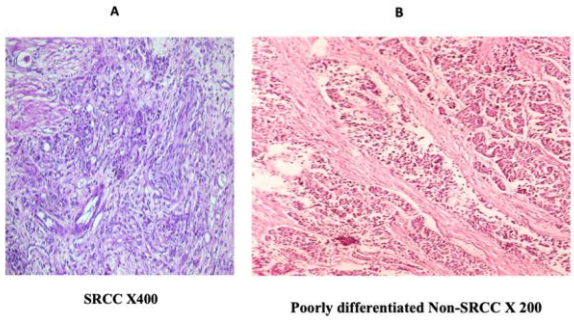

Figure 3: Microscopic picture of SRCC and Non-SRCC by Hx&E (A & B).

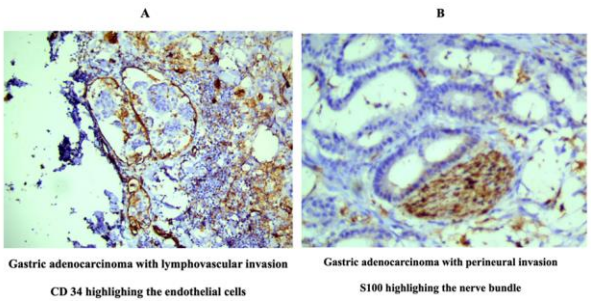

Figure 4: Microscopic picture of gastric adenocarcinoma with immunostain CD34 & S100 (A&B)

Results:

This is prospective cohort study including 68 adenocarcinoma gastric cancer patients, 42 with non-SRCC and 26 with SRCC, the study included 46 males 28 of them with non-SRCC and 22 females 14 of them with non-SRCC, the mean age of non-SRCC patients is 51.5 years while the mean age among SRCC patients is 48 years. All patients had Eastern Cooperative Oncology Group Performance Status (ECOG PS) 1 with the exception of 6 patients had ECOG PS 2, all patients had advanced T stage, 30 patients had T3 tumor, 18 with non-SRCC and 12 with SRC, while 38

patients had T4 tumor , 24 with non-SRCC and 14 with SCR.

36 patients received chemoradiotherapy, 26 as adjuvant post-operative and 10 as radical for advanced inoperable cases, 20 patients non-SRCC and 16 SRCC. 32 patients received palliative chemotherapy Capeox protocol for metastatic disease, 22 non-SRCC and 10 SRCC.

There wasn't any significant differences regarding sex, age, tumor size, depth of invasion and regional lymph node involvement (Table 1).

Regarding the metastatic sites, the only statistically significant finding was the presence of ascites, p-value = 0.031(Table 2), however this finding was clinically irrelevant due to the small difference in patient number presented with ascites in both groups, 5 non-SRCC and and 6 SRCC.

Coming to survival rates there wasn't any significant difference between non-SRCC and SRCC, the one year OS was 18% for non-SRCC and 17 % for SRCC while the two year OS was 5% and 4% respectively, the median OS for non-SRCC was 7 months and for SRCC was 7.5 months with p-value = 0.669 (Figure 5).

While the one year PFS reached 30% in non-SRCC and 18% for SRC, and the two year PFS was 11% for non-SRCC and 10% for SRC, the median PFS for non-SRCC reached 5 months and 5.5 months for SRC with p-value=0.494 (Figure 6).

However when we compared between T3 and T4 regardless of the pathology in both groups patients with T3 tumors had a marked better OS than T4 patients, the one year OS was 23% for patients with T3 tumors and 4% for T4 tumors regardless of the pathology, while the two year OS for patients with T3 tumors was 11% and 0% for T4 tumors with p-value= 0.005, pointing to the fact that tumor stage has more impact on survival rather than the pathology type in our study (Figure 7).

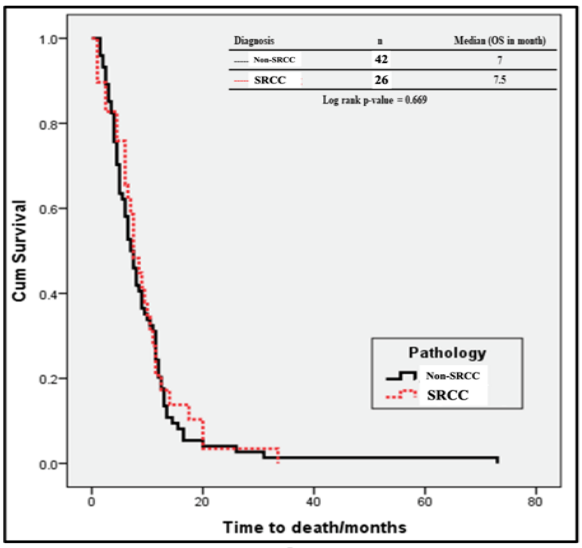

Figure 5: The OS of Non-SRCC & SRCC patients
OS % at one year (non-SRCC =18% & SRCC =17%)
OS % at two years (non-SRCC =5% & SRCC =4%)

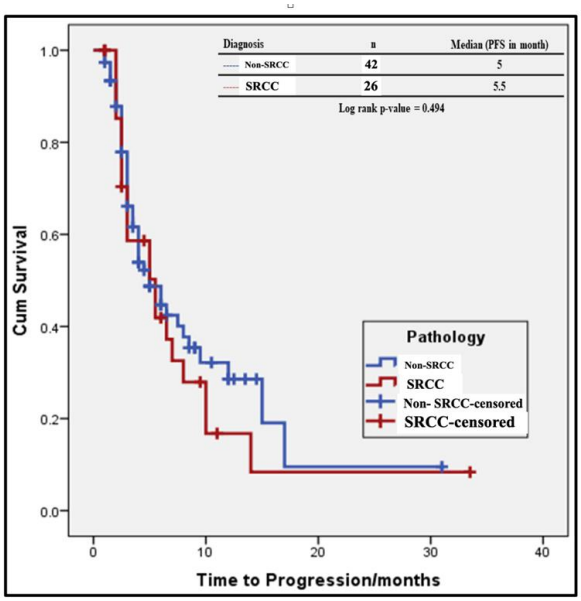

Figure 6: The PFS of Non-SRCC & SRCC patients
PFS % at one year (non-SRCC =30% & SRCC =18%)
PFS % at two years (non-SRCC =11% & SRCC =10%)

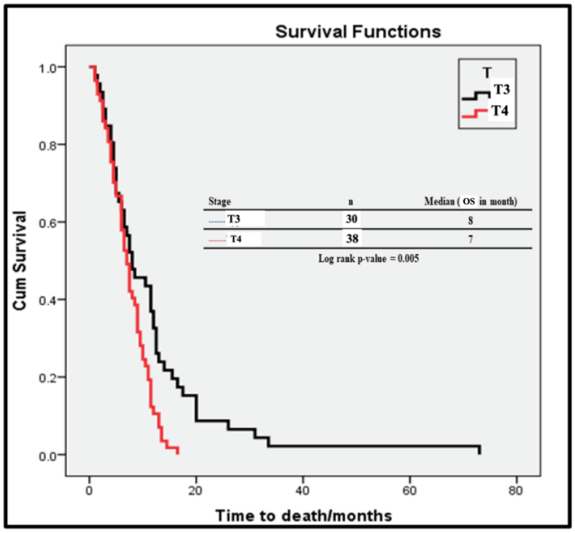

Figure 7: The OS of patients with T3 & T4 tumors in both pathological groups
OS % at one year (T3 =23% & T4 =4%) in both pathological groups
OS % at two years (T3=11% & T4=0%) in both pathological groups

Table 1: Baseline Clinical Characteristics of Non-SRCC & SRCC

	Non-SRCC (n = 42)	SRCC (n = 26)	P-value
Age in years Mean ± SD	51.564 ± 13.1	48.00 ± 11.4	= 0.197*
Sex			
- Male	28(66.7%)	18 (69.2%)	= 0.323**
- Female	14 (33.3%)	8 (30.8%)	
ECOG PS			
- 1	38 (90.5%)	24 (92.3%)	= 0.529**
- >1	4 (9.5%)	2 (7.7%)	
Tumor stage			
- T3	18 (42.9%)	12 (46.2%)	= 0.825**
- T4	24 (57.1%)	14 (53.8%)	
Nodal stage			
- N0	3(7.1%)	2(7.7%)	
- N1	4 (9.5%)	2 (7.7%)	= 0.405**
- N2	22(52.4%)	14 (53.8%)	
- N3	13 (31%)	8 (30.8%)	
Radical Surgery			
- No	28(66.7%)	14(53.8%)	=0.884**
- Yes	14(33.3%)	12 (46.2%)	
Adjuvant Intergroup			
- No	28(66.7%)	14(53.8%)	=0.430**
- Yes	14(33.3%)	12(46.2%)	
Radical chemoradiation			
- No	36(85.7%)	22(84.6%)	= 0.834**
- Yes	6(14.3%)	4(15.4%)	
Palliative chemotherapy			
- No	14(33.3%)	12(46.1%)	=0.741****
- Metastatic	22(52.4%)	10(38.5%)	
- Unresectable	6 (14.3%)	4(15.4%)	

*T-test analysis was used to compare the mean difference between the two groups

**Chi-square Test analysis was used to compare the difference in proportions

ECOG PS = Eastern Cooperative Oncology Group Performance Status, SD = Standard deviation

Table 2: Local and distant Metastasis of Non-SRCC & SRCC

	Non-SRCC (n = 42)	SRCC (n = 26)	P-value*
Metastastatic			
- No	20(47.6%)	16(61.5%)	= 0.430
- Yes	22(52.4%)	10(38.5%)	
Locally advanced			
- No	36(85.7%)	22(84.6%)	= 0.272
- Yes	6(14.3%)	4(15.4%)	
HFLs			
- No	29(69%)	20 (76.9%)	= 0.053
- Yes	13(31%)	6(23.1%)	
Ascites			
- No	37(88.1%)	20(76.9%)	= 0.031
- Yes	5 (11.9%)	6 (23.1%)	
Omental Metastasis			
- No	32(76.2%)	14(66.7%)	= 0.485
- Yes	10 (23.8%)	12(33.3%)	
Lung Metastasis			
- No	38(90.5%)	19(73.1%)	= 0.202
- Yes	4(9.5%)	7(26.9%)	

*Chi-square Test analysis was used to compare the difference in proportions

HFLs = Hepatic focal lesions

Discussion:

This is a prospective cohort study aiming to compare the prognosis and outcome of SRCC in gastric cancer with respect PFS and OS. While there′s been a decline in the incidence of gastric cancer worldwide in recent years which is the results of the efficient diagnosis and eradication of helicobacter pylori, on the other side the incidence of SRC is increasing and this should point the attention towards risk factors for SRCC in particular including germline mutations in CDH1 gene [4].

Our study included 68 gastric cancer patients, 42 with non-SRCC and 26 with signet ring carcinoma, 46 males 28 of them with non-SRCC and 22 females 14 of them with non-SRCC, with mean age 51.5 among non-SRCC patients and mean age 48 among SRCC patients. There was a male sex predilection seen in both groups, however it wasn't statistically significant, p=0.323. Neither of the other clinical and disease related characteristics reached any level of significance with the exception of the presence of ascites p=0.031, however clinically it was irrelevant as only 5 patients (11.5%) with non-SRCC and 6 patients (23.1%) with SRCC had ascites. Hyung et al reported a female and a young age predilection among patients with SRC, which didn't agree with our study [19].

Patients included in our study had advanced T stage (T3 and T4) which was a good advantage to restrict the comparison between the two pathological types excluding early stages, however survival analysis showed no statistically significant difference between non-SRCC and SRCC patients, the one year OS was 18% for non-SRCC and 17 % for SRCC while the two year OS was 5% and 4% respectively, the median OS for non-SRCC was 7 months and for SRCC was 7.5 months with p-value = 0.669 (Figure 5), the same findings with PFS as the one year PFS reached 30% in non-SRCC and 18% for SRC, and two year PFS was 11% for non-SRCC and 10% for SRC, the median PFS for non-SRCC reached 5 months and 5.5 months for SRC with p-value=0.494 (Figure 6).

The fact that patients included in our study had advanced tumor stage T3 and T4 may be justified by the late diagnosis of gastric cancer in our community as many patients seek medical advice after years of neglected symptoms.

In our study tumor stage had more impact on survival rather than pathology type as shown in (Figure 7) which shows patients with T3 had a better OS than those with T4 whatever the pathology was, patients with T3 tumors had a marked better OS than T4 patients, the one year OS was 23% for patients with T3 tumors and 4% for T4 tumors regardless of the pathology, while the two year OS for patients with T3 tumors was 11% and 0% for T4 tumors with p-value= 0.005, this pointed the attention in further studies to compare different pathology types among patients after adjustment of disease stage.

Kang SH et al. reported that the prognosis of early stage gastric SRC in most studies was equivalent to or better than that of other gastric adenocarcinomas non-

SRCC. However, in advanced gastric cancer, prognosis of gastric SRC is more controversial and is commonly considered to be poor compared to that of non-SRCC [12].

Furthermore, Messager M et al. reported that chemosensitivity of SRCC to specific protocols needs to be identified with the evaluation of the use of peri-operative therapy or taxane based chemotherapy [15].

Finally, Heger et al considered SRCC to be an independent prognostic factor after adjustment of disease stage, which didn't agree with our study while others suggest the contrary and contradicted the prognostic role of SRCC, so in conclusion, the prognosis of SRCC in advanced gastric cancer is still controversial and needs further multicentre studies [20].

Conclusion:

This study failed to show any significant difference between non-SRCC and SRCC regarding OS and PFS despite the obvious difference in tumor biology and behavior which may be attributed to the relative smaller number of patients represented with SRCC compared to non-SRCC and the small number of the study group as a whole.

In addition patients with T3 tumor had a statistically significant better OS than those with T4 pointing to the fact that tumor stage has more impact on disease outcome than the pathology being SRCC or non-SRCC, so whether to adopt these results or not will depend on further results from other prospective multicenter studies with adjustment of disease stage.

List of abbreviations

CAPEOX = Capecitabine/Oxaliplatin
CTV = Clinical target volume
EBV = Epstein Barr virus
ECOG PS = Eastern Cooperative Oncology Group Performance Status
GTV = Gross tumor volume
Gy = Gray
HFLs = Hepatic focal lesions
Hx&E = Hematoxylin and eosin
IBM Inc. = International Business Machines incorporation
IDC = Invasive ductal carcinoma
JGCA = Japanese Gastric Cancer Association
MS/CT = Multislice/Computed Tomography
MSI = Microsatellite instability
MV = Mega-voltage
Non-SRCC = Non-signet ring cell carcinoma
OS = overall survival
PET/CT = Positron Emission Tomography/Computed Tomography
PFS = Progression free survival
SD = Standard deviation
SECI = South Egypt Cancer Institute
SRCC = Signet ring cell carcinoma
TCGA = The Cancer Genome Atlas
TNM = Tumor Nodal Metastasis
USA = United States of America
WHO = World health organization

Competing interests

The authors declare that they have no conflict of interests.

Acknowledgments

This work was supported by fund from the research unit of South Egypt Cancer Institute.

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