

## Appendix 1 Summary of the findings from published studies on gastric signet ring cell cancer

Study, country, period	Main inclusion criteria	N	SRCC%	Main findings: 1. Factors associated with more SRCC; 2. Prognostic factors identified by univariate analysis; 3. Prognostic factors identified by multivariate analysis
Arsene 1995, France, 1978-1987[1]	All gastric cancer	999	20-34%	1. Not investigated; 2. Not investigated; 3. >75 years, invaded resection margins, lymph node involvement, metastasis, parietal wall involvement (for SRCC, HR not available, p>0.05)
Bamboato 2014, USA, 1990-2009[2]	Curatively resected gastric cancer	569	37%	1. Younger age, female, proximal/body region of stomach, serosal involvement, higher TNM stage; 2. histological type, tumor location, TNM stage, tumor size, number of positive node, adjuvant chemotherapy (for SRCC, HR not available, p<0.05); 3. Location, number of positive nodes (for SRCC, HR not available, p<0.05)
Bu 2013, China, 2004-2009[3]	Mucinous gastric cancer or SRCC undergoing surgery	181	59.1%	1. Younger age, stage I-II, middle and lower thirds and total stomach, smaller tumor size, negative lymph node metastasis, negative lymphatic vascular invasion; 2. Not investigated; 3. Not investigated
Chen 2014, China, 2004-2008[4]	Curatively resected gastric cancer	991	14.2%	1. Younger age, female, middle and lower thirds and total stomach, Bormann type IV, Lauren type diffuse, poor differentiation, later TNM stage; 2. Tumor location, gastrectomy, Bormann type, tumor size, histological type, Lauren type, tumor differentiation, vessel invasion, perineural invasion, TNM stage, adjuvant chemotherapy (for SRCC, HR not available, p<0.001); 3. Bormann type, histological type, vessel invasion, TNM stage, adjuvant chemotherapy (for SRCC, HR 1.072, 95% CI 1.001-1.147, p<0.001)
Choi 1996, Korea, --[5]	Curatively resected locally advanced gastric cancer	697	--	1. Younger age; 2. Not investigated; 3. Not investigated
Cui 2015, China, 2003-2007[6]	Curatively resected gastric cancer with complete clinical information	1447	19.9%	1. Female, middle and lower thirds and total stomach, later T stage, later TNM stage, metastasis, total resection; 2. Age, tumor size, location, Bormann type, histological type, TNM stage, resection type, adjuvant chemotherapy (for SRCC RR not available, p<0.001); 3. Age, tumor size, histological type, TNM stage, Bormann type, adjuvant chemotherapy (for non-SRCC vs SRCC, RR=0.606, 95% CI 0.511-0.718, p<0.001)
Dittmar 2015, Germany, 1994-2011[7]	Curatively resected node-negative gastric cancer	228	39.6%	1. Not investigated; 2. Sex, T category, lymphangiogenesis, tumor differentiation, serosal infiltration, histological growth pattern, tumor size and Lauren type (for SRCC: HR not available, p>0.05); 3. Tumor size, sex (for SRCC: HR not available, p>0.05)
Fang 2009, Taiwan, 1987-2005[8]	Curatively resected mucinous gastric cancer or SRCC	176	7.9%	1. Female, smaller tumor size, less deep cancer invasion; 2. Histological type (in early gastric cancer, HR for SRCC vs mucinous <1, p=0.012; in advanced gastric cancer, HR not available, p>0.05); 3. Not investigated
Gill 2003, Canada, 1978-1997[9]	Gastric adenocarcinoma	2043	--	1. Asian; 2. No details (for SRCC: HR not available, p>0.05); 3. Tumor location, differentiation, extent of disease, resection, palliative chemotherapy (SRCC: not investigated)
Ha 2008, Korea, 1994-2001[10]	Curatively resected early gastric cancer	1520	25.5%	1. Female, younger age, less deep invasion, smaller tumor size, negative lymph node metastasis, negative lymphatic involvement; 2. Not investigated; 3. Not investigated
Hass 2011, Germany, 2003-2007[11]	All gastric cancer	160	27.5%	1. Female, younger age, diffuse subtype, poor differentiation, corpus area, faster recurrence, metastasis; 2. Not investigated; 3. Tumor stage (for SRCC: not investigated)
Heger 2014, Germany, 1987-2011[12]	Locally advanced esophagogastric adenocarcinoma treated with neoadjuvant therapy	723	32.5%	1. Female, gastric localization, advanced T category, Lauren type of diffuse/ non-intestinal histology, lower clinical response, no complication, no surgical complication, lower probability of curative resection; 2. Histological type, grading, localization, Lauren type, clinical response, complications, surgical complications, TNM stage, resection type (for SRCC: HR not available, P<0.001); 3. Clinical response, complications, surgical complications, TNM stage (for SRCC: HR not available, p>0.05)

Huh 2013, Korea, 1999-2005[13]	Early gastric cancer undergoing surgery	2208	24.4%	1. Younger age, female, location of mid-body, mucosa-confined, depressed type, lower lymph node metastasis, lower lymphovascular invasion; 2. SRCC associated with better survival, HR not available, p=0.002; 3. Not investigated
Hyung 2002, Korea, 1987-1995[14]	Early gastric cancer undergoing gastrectomy	933	28.2%	1. Female, younger age, middle and lower stomach, depressed macroscopic type, less deep invasion, no lymph node metastasis, fewer number of involved lymph node; 2. SRCC associated with better survival, HR not available, p=0.01; 3. Not investigated
Jiang 2011, China, 1980-2004[15]	All gastric cancer undergoing gastrectomy	2315	9.1%	1. In early gastric cancer: younger age, female, less deep invasion; in advanced gastric cancer: younger age, male, larger tumor size, Borrmann type III-IV, deeper invasion, negative peritoneal dissemination, curative; 2. Not investigated; 3. In early gastric cancer: age, lymphovascular invasion, curability (for SRCC: RR=2.36, p=0.01); in advanced gastric cancer: age, tumor size, tumor location, macroscopic type, depth of invasion, lymphovascular invasion, lymph node metastasis, hepatic metastasis, peritoneal dissemination, curability (for SRCC: RR=1.171, p=0.085)
Jiang 2013, China, 1997-2007[16]	Mucinous gastric cancer or SRCC undergoing gastrectomy	368	11.8%	1. Middle and lower stomach, no distant metastasis, D2 and above lymph node dissection, less deep invasion, advanced Borrmann type, early TNM stage, early lymph node status; 2. No details (for SRCC: HR not available, p=0.064); 3. Not investigated
Jin 2015, USA, 2000-2012[17]	Curatively resected lymph node negative gastric cancer	805	33%	1. Not investigated; 2. Not investigated; 3. T stage, tumor size, histological grade, histological type, number of lymph node examined, lymphovascular invasion, perineural invasion (for SRCC: HR=2.1, p=0.01)
Kim 1994, Korea, 1981-1991[18]	All gastric cancer undergoing surgery	3702	12.2%	1. In early gastric cancer: younger age, female, middle-third stomach, less deep invasion, fewer lymph nodes metastasis; in advanced gastric cancer: younger age, female, large tumor size, middle-third stomach, deeper invasion, more lymph nodes metastasis; 2. Not investigated; 3. In early gastric cancer: SRCC not associated with prognosis (HR not available); in advanced gastric cancer: SRCC associated with worse prognosis (HR not available)
Kim 2004, Korea, 1980-1999[19]	All gastric cancer undergoing surgery	2358	8.7%	1. Younger age, smaller tumor size, early T stage, negative lymph node invasion, negative hepatic metastasis, early stage, curative; 2. Not investigated; 3. Lymph node metastasis, curability (for SRCC: RR=0.948, p>0.05)
Kim 2005, Korea, 1986-2000[20]	Gastric cancer aged <36 years or >70 years	2014	3.1-18.3%	1. Not investigated; 2. In those aged >75 years: tumor size, depth of invasion, differentiation, operation type, lymph node invasion (for SRCC: not investigated); 3. In those aged >75 years: differentiation, curability, lymph node metastasis (for SRCC: not investigated)
Kim 2014, Korea, 2002-2008[21]	Curatively resected gastric cancer	224	4.5-12.5%	1. Not investigated; 2. Not investigated; 3. Not investigated
Kunisaki 2004, Japan, 1980-1998[22]	Curatively resected gastric cancer	1113	15.6%	1. In early gastric cancer: Younger age, female, middle third stomach, larger tumor size, depressed type of lesion; in advanced gastric cancer: younger age, female, poor differentiation, middle third stomach, smaller tumor size; 2. In early gastric cancer: age, macroscopic appearance, depth of invasion, histological type, number of lymph node involved (for SRCC: HR=4.88, p=0.008); in advanced gastric cancer: age, tumor location, macroscopic appearance, tumor size, depth of invasion, number of lymph node involved, lymphatic invasion, venous invasion (for SRCC: HR not available, p>0.05); 3. In early gastric cancer: age, number of lymph node involved, (for SRCC: HR=3.56, p=0.036); in advanced gastric cancer: age, tumor size, depth of invasion, number of lymph node involved, venous invasion (for SRCC: not investigated)
Kwon 2013, Korea,	Gastric adenocarcinoma	769	14.0%	1. In early gastric cancer: younger age, female, perineural invasion, flat or depressed macroscopic type,

1999-2009[23]	undergoing surgery			larger tumor size, middle or lower stomach; in advanced gastric cancer: younger age, female, middle or lower stomach, flat or depressed macroscopic type, perineural invasion, no hepatic metastasis; 2. In early gastric cancer: age, TNM stage (for SRCC HR=0.869, p=0.824); in advanced gastric cancer: age, tumor size, venous invasion, perineural invasion, lymphovascular invasion, TNM stage, chemotherapy, surgery type (for SRCC: HR=0.925, p=0.750); 3. In early gastric cancer: age, TNM stage (SRCC: not investigated); in advanced gastric cancer: age, TNM stage, surgery type (SRCC: not investigated)
Lee 2012, Japan, 1989-2005[24]	Gastric adenocarcinoma undergoing gastrectomy accompanied by lymph node dissection	1376	23.3%	1. Younger age, smaller tumor size, Lauren type of diffuse, no lymphatic invasion, no vascular invasion, no perineural invasion, less deep invasion, less lymph node metastasis, early pathological type; 2. SRCC associated with better survival (HR not available, p<0.05); 3. Age, gender, depth of invasion, lymph node metastasis, curability (for SRCC: HR not available, p>0.05)
Lee 2013, Korea, 2003-2005[25]	Node-negative advanced gastric cancer undergoing curative gastrectomy with extended lymphadenectomy	424	--	1. Not investigated; 2. Depth of invasion, differentiation, tumor size, histological type (for SRCC: HR=2.65, p<0.02); 3. Differentiation, depth of invasion (SRCC: not investigated)
Lee 2015, Korea, 2003-2011[26]	Early gastric cancer undergoing curative gastrectomy with lymph node dissection	696	16.4%	1. Female, younger age, middle stomach, flat or depressed macroscopic type; 2. Not investigated; 3. Not investigated
Li 2007, China, 1987-2003[27]	All advanced gastric cancer undergoing surgery	4759	13.9%	1. Larger tumor size, advanced Borrmann types, deeper invasion, more lymph node metastasis, negative perineural invasion, advanced stage, noncurative; 2. Not investigated; 3. Depth of invasion, lymph node metastasis, hepatic metastasis, peritoneal dissemination, curability (for SRCC RR=1.016, p=0.219)
Maehara 1992, Japan, 1965-1985[28]	Gastric cancer undergoing gastrectomy	1500	3.4%	1. In early gastric cancer: younger age, female, larger tumor size; in advanced gastric cancer: younger age, female, less prominent serosal invasion; 2. SRCC with better prognosis (HR not available, p<0.01); 3. Not investigated
Nered 2006, Russia, --[29]	Gastric cancer undergoing gastrectomy	372	16.1%	1. Younger age, female, less lymph node metastasis, more involvement of perigastric fatty tissue, peritoneum and ovary; 2. Not investigated; 3. Not investigated
Otsuji 1998, Japan, 1970-1994[30]	Gastric cancer undergoing gastrectomy	1498	10.3%	1. In early gastric cancer: female, middle stomach, more IIc and less I/IIa type of gross appearance; in advanced gastric cancer: bigger tumor size, more peritoneal metastasis, more extended radical lymph node dissection and curative surgery; 2. In early gastric cancer: SRCC associated with better survival (HR not available, p<0.05); in advanced gastric cancer: for SRCC, p>0.05; 3. Not investigated
Park 2008, Korea, 1983-2002[31]	Gastric cancer undergoing gastrectomy	2275	11.0%	1. Younger age, female, middle stomach, greater surgical curability, early T/N stage; 2. Not investigated; 3. In stage IV gastric cancer: curative resection, number of dissected lymph nodes, gender, Borrmann type, histological type (for SRCC: RR=1.872, p=0.001)
Park 2009, Korea, 2000-2005[32]	All gastric cancer	3362	16.4%	1. Younger age; 2. Tumor location, Lauren type, depth of invasion, lymph node involvement, TNM stage, metastasis of liver/peritoneum/other distant tissue, type of resection, curative resection, lymphatic invasion, vein invasion, CA19-9, CEA (for SRCC: HR and p not available); 3. Stage, vein invasion, curative resection, CA19-9 (for SRCC: HR and p not available)
Piessen 2009, France, 1996-2007[33]	Advanced gastric cancer undergoing surgery	215	27.4%	1. No macroscopic aspect of linitis plastica, advanced N category, more lymph node involvement, less curative resection, positive proximal margin, positive distant margin; 2. ASA grade, weight loss, nonantro-

				pyloric tumoral location, macroscopic aspect of linitis plastica, enlarged resection to neighboring organ, incomplete resection, depth of invasion, lymph node invasion, advanced TNM stage (for SRCC: HR not available, p=0.004); 3. TNM stage, nonantro-pyloric tumoral location, histological type (for SRCC: HR=1.5, p=0.004)
Postlewait 2015, USA, 2000-2012[34]	All gastric adenocarcinoma undergoing curative-intent resection	768	40.6%	1. Female, younger age, poor differentiation, perineural invasion, microscopically positive resection, distal location, adjuvant therapy, more advanced stage, earlier recurrence; 2. For SRCC: HR not available, p=0.011; 3. Tumor size, perineural invasion, TNM stage, adjuvant therapy (for SRCC: HR=0.75, p=0.095)
Shim 2014, Korea, 1998-2005[35]	Gastric adenocarcinoma undergoing curative gastrectomy	2643	14.3%	1. Younger age, female, open approach, middle stomach, shorter proximal margin, less depth of invasion, less advanced stage, no adjuvant therapy, no recurrence; 2. Gender, age, resection extent, tumor location, tumor size, proximal margin, lymph node status, depth of invasion, stage, adjuvant therapy, recurrence (for SRCC: HR=0.83, p=0.1232); 3. Age, resection extent, adjuvant therapy, recurrence (for SRCC: HR=1.16, p=0.3298)
Shridhar 2013, USA, 2004-2008[36]	Metastatic gastric adenocarcinoma, diffuse carcinoma or signet ring cell carcinoma with known information on status of surgery and radiation therapy	5072	7.3%	1. Not investigated; 2. Not investigated; 3. Age, surgery, radiation, TNM stage (for SRCC HR=1.218, p=0.002)
Sirohi 2014, India, 2012-2013[37]	Advanced gastric cancer	128	37.5%	1. Not investigated; 2. Performance status, type of chemotherapy, number of chemotherapy drugs used, second-line therapy (SRCC: not investigated); 3. Performance status, type of chemotherapy (SRCC: not investigated)
Taghavi 2012, USA, 2004-2007[38]	All adenocarcinoma and SRC with complete information	10246	26.0	1. Younger age, female, stage T3-4, lymph node involvement, distant metastasis, lower and middle stomach; 2. Age, race, surgical resection, AJCC stage, TNM stage, radiation therapy (for SRCC: HR=1.06, p=0.07); 3. Stratified by radiation and AJCC stage: age, race, surgical resection (for SRCC: HR=1.05, p=0.150)
Theuer 1999, USA, 1984-1994[39]	All gastric cancer	3020	15%	1. Younger age, female, distal stomach; 2. Not investigated; 3. For SRCC: RR=1.027, p>0.1
Triboulet 2013, France, 1997-2010[40]	pTis or pT1 adenocarcinoma tumor	421	24.7%	1. Younger age, non-extensive surgical resection, submucosa; Not investigated; 3. Not investigated
Walker 1996, USA, 1978-1994[41]	All gastric carcinoma, excluding lymphoma and sarcoma	192	9%	1. Younger age; 2. Not investigated; 3. Not investigated
Yao 2005, USA, 1985-1999[42]	Invasive gastric cancer	1987	30.6%	1. White people; 2. Race, tumor stage, WHO histological type, tumor location, age (for SRCC HR=1.36, p<0.01); 3. Race, tumor stage, WHO histological type, tumor location, age (for SRCC HR=1.34, p=0.01)
Yokota 1998, Japan, 1985-1995[43]	Gastric carcinoma	683	10.1%	1. Younger age, female, larger tumor size, infiltrative growth pattern, scirrhous cancer-stromal relationship; 2. In early gastric cancer: no difference in survival between SRCC vs non-SRCC; in advanced gastric cancer: SRCC associated with poorer prognosis; 3. Not investigated
Yoon 2010, USA, 1980-1997[44]	Adenocarcinoma of esophagus, gastroesophageal junction, or gastric cardia undergoing complete tumor	796	--	1. Not investigated; 2. Age, TNM stage, tumor grade, SRCC, extracapsular lymph node (for SRCC: HR=1.58, p<0.001); 3. Age, TNM stage, preoperative chemotherapy or radiotherapy (SRCC: not investigated)

	resection			
Zhang 2010, China, 1993-2003[45]	All gastric cancer undergoing surgery	1439	15.1%	1. Smaller tumor size, middle stomach, advanced Borrmann type, less depth of invasion, less lymph node metastasis, less advanced stage, less lymphatic invasion, less curability, no chemotherapy; 2. For SRCC: HR not available, p=0.013; 3. Tumor size, serosal invasion, lymph node metastasis, curative resection (non-SRCC vs SRCC: RR=1.263, p=0.068)
Zheng 2010, Japan, -- [46]	All gastric adenocarcinoma	--	--	1. Younger age, female, weaker expression of ki-67, CPP32, p53, parafibromin, GRP78, GRP94, P-GSK3β-ser9, VEGF or cortactin; 2. Not investigated; 3. Differentiation, mucinous subtype, age, invasion depth, lymphatic invasion, peritoneal dissemination, WHO classification (for SRCC HR and p not available)

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