



Resection line involvement after gastric cancer treatment: handle with care

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Abstract

The optimal management of patients with resection line involvement after endoscopic or surgical treatment for gastric cancer is debated. In contrast to previous reports, we examined both the experience of endoscopists and surgeons in early-stage lesions and the wide variation in treatments proposed for advanced disease in case of infiltration of resection margins. A PubMed search for papers using the key words: gastric or stomach cancer, or Carcinoma; gastrectomy and positive margins; surgical margins or resection line or endoscopic margin involvement; and R1 resection, from January 2000 to July 2015 was undertaken. Fifty-three studies were considered pertinent to the study. Many endoscopists report that some cases of early gastric cancer with resection line involvement after endoscopic resection have good outcomes notwithstanding incomplete resection, but few surgeons share this opinion. Conversely, it is unanimously agreed that very advanced stages should not be surgically retreated because they are expression of systemic disease. Between early and very advanced cancer the usefulness of re-resection for microscopic resection lines involvement is still debated and surgery may be proposed only when radicality can be achieved. When surgery is not feasible, radiochemotherapy may represent a valid alternative.

Keywords Resection line involvement · Infiltrated resection margin · Gastric cancer · Frozen section · Endoscopic submucosal dissection · R1 resection · Radiochemotherapy

Introduction

Microscopic involvement after apparently radical resection of gastric cancer (RLI) is observed in 2.8–20% of gastric resections [1, 2] and it is always considered a difficult situation to manage. Although several retrospective studies and a number of reviews have focused on this problem, there are still no definitive guidelines for treatment because of the few cases considered and the obvious lack of perspective studies or randomized trials carried out in this area.

In recent years, several endoscopic studies have evaluated RLI in early gastric cancer (EGC), some focusing on large

patient populations with long follow-up. Also many surgical reports on this topic exist. However, to our knowledge, no studies dealing with both endoscopic and surgical point of views have been published to date. Whilst endoscopists only consider surgical options for some cases of incomplete resection, proposing follow-up strategies in the remaining patients, surgical studies generally propose re-resection for early-stage gastric cancer. The issue of new surgical resection in advanced gastric cancer patients when RLI is confirmed in the definitive pathology report is still debated. The aim of the present review is to report all the existing evidences on the management of RLI after endoscopic or surgical treatment for gastric cancer and to assess the optimal strategy to be adopted in this challenging situation in different clinical scenarios.

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

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Literature search

We performed a literature search in PubMed for English-language studies published from January 2000 to July 2015 using the key words: gastric or stomach cancer, or

carcinoma; gastrectomy and positive margins; surgical margins or resection line or endoscopic margin involvement; and R1 resection. Fifty-three studies were considered pertinent to the study. Eighty studies were collected of which 3 were review articles. Twenty-four were excluded because they did not completely focus on RLI. Fifty-three studies were considered pertinent to the subject matter, 15 studies were of relevant endoscopic interest, and 38 were written by surgeons. All the articles were discussed by the authors to determine their suitability for inclusion. We also examined the studies referred to in the three reviews identified [3–5] and took into account the conclusions of a Web Round Table organized before the 10th International Gastric Cancer Congress (IGCC) held in Verona in 2013 involving endoscopists and surgeons. Information about the conclusions of the Web Round Table is reported in *Gastric Cancer* [6].

Risk factors for resection line involvement

Endoscopists frequently reported a higher incidence of RLI when criteria for indication to endoscopic resection were not completely fulfilled. Non-differentiated cancer, size, T stage and lesion sites with technical problems were reported as risk factors for resection line involvement in multivariate analyses (Table 1). Of note, risk factors for RLI were similar also after surgical resection (Table 2). However, Bissolati et al. differentiated risk factors in relation to Lauren’s classification [26]; they found that in locally advanced gastric cancer with Lauren intestinal histology, serosal invasion, cardia location, and a margin distance of < 3 cm were independent risk factors, while in diffuse/mixed tumor types, lymphatic infiltration, tumor diameter > 4 cm, esophagogastric junction location and serosal invasion were significantly associated with a high RLI risk.

Indications for safe resection margins in gastric cancer treatment

When endoscopic criteria for resection were met, endoscopists generally consider a distance of 5–10 mm from the lesion as adequate resection margins. With regard to surgical resection, guidelines differ from country to country; the definition of correct margins range from 2 to 8 cm from the tumor [27–30], chosen on the basis of cancer stage and pathological and gross type (Table 3).

Indications for frozen section

When the distance from the margin did not respect guidelines and/or risk factors for RLI are present, i.e., serosal or lymphatic invasion, esophagogastric junction location, diffuse type, and size > 4 cm (complete list is reported at Table 2), frozen sections are always indicated if a new, wider resection is immediately achievable [38, 39]. However, false negatives were reported [24], especially in diffuse or mixed tumors.

Resection line as a prognostic risk factor

None of the studies by endoscopists in early gastric cancer considered incomplete endoscopic resection as a significant prognostic factor; an endoscopic re-resection or surgery is indicated without doubt only in patients with vertical or massive lateral margin involvement [18, 29]. Close follow-up is indicated in cases of limited lateral margin involvement without any other risk factor for nodal metastases [8]. This differs greatly from surgical studies. Indeed, all but two [40, 41] of the studies evaluating prognostic impact of RLI after surgery for gastric cancer considered it as a negative prognostic factor even in early stages of disease (Table 4). Specifically, for early lesions (pT1 or pT2), a very poor prognosis is generally reported in case of RLI compared to cases with pathologically clear resection

Table 1 Multivariate analysis of risk factors for RLI in endoscopic patients

References	Tumor size	Tumor location	Undifferentiated histology	Signet ring cell	Associated severe metaplasia	Submucosal invasion	Technical problems	Absolute ESD criteria respected	Recurrence type
Kakushima et al. [7].	0.0067		0.016			0.007			0.014
Numata et al. [8]		<0.01						<0.05	
Yun et al. [9]			0.01	0.009	0.024		<0.001		

RLI resection line infiltration

Table 2 Risk factors for RLJ in surgical patients

References	Tumor size	Tumor location	Signet ring cell	pT	pN	Total no. N+	Grading	Lauren's histotype	Bormann type	Peritoneal metastasis	Extranodal metastasis
Songun et al. [10]		X	X	X			X				
Cascinu et al. [11].		X					X				
Kim et al. [12]		X		X	X	X		X			
Chan et al. [13]				X	X						
Shen et al. [14]	X			X							
Cho et al. [2]		X	X	X	X	X	X		X		
Morgagni et al. [15]				X				X			
Sun et al. [16]	X			X	X					X	
Wang et al. [17]	X			X	X						
Nagata et al. [18]	X			X	X						
Kim et al. [19]		X						X			
Lee et al. [1]	X	X	X						X		
Bickenbach et al. [20]				X	X	X					
Stiekema et al. [21]								X			
Kim et al. [22]				X	X		X				
Liang et al. [23]									X		X
Squires et al. [24]	X	X	X								
Woo et al. [25]	X										
Bissolati et al. [26]	X	X		X	X			X			

Table 3 National guidelines on resection margins

National guidelines	Indication
English [31]	Ex vivo 3.5 cm
France [32]	If R0 margins achievable, no distance required
German [33]	5 cm if intestinal Lauren's histologic type, 8 cm if diffuse
Japanese [34]	2 cm for T1, 3 cm for T2/expansive cancer and 5 cm for T3/4 or infiltrating cancer
ESSO ESMO [35]	5 cm, if diffuse type 8 cm
Italian [36]	2 cm for T1, 3 cm for T2/intestinal/expansive cancer and 5 cm for T3/4 or infiltrating cancer
NCCN [37]	4 cm for T1/T3

Table 4 RLI as prognostic factor of overall survival

References	Univariate	Multivariate	Significance in subgroups
Songun et al. [10]	$P < 0.001$	$P = 0.001$	
Cascinu et al. [11]	Significant	–	pN: N0
Kim et al. [12]	$P < 0.0001$	$P = 0.003$	N: $N + \leq 5$
Chan et al. [13]	$P < 0.001$	$P < 0.001$	
Mariette et al. [42]	$P = 0.02$	$P = 0.03$	
Dicken et al. [43]	$P < 0.001$	$P < 0.014$	
Shen et al. [14]	$P < 0.001$	ns	Stage: I, II
Cho et al. [2]	$P = 0.0028$		pN: N0
Lello et al. [44]	Significant	$P = 0.001$	
Morgagni et al. [15].	$P < 0.0001$	$P = 0.014$	pN: T2, T3
Piessen et al. [45]	$P < 0.001$	ns	
Sun et al. [16]	$P < 0.001$	ns	pT, pN: T1, T2, N0, N1, stage I, stage II
Wang et al. [17].	$P < 0.0001$		
Nagata et al. [18]	$P < 0.0001$	$P = 0.0059$	
Chen et al. [46]	$P = 0.019$	$P = 0.048$	D: $D \geq 2$ pN: $N \leq 2$
Zhang et al. [40]	ns		
Bickenbach et al. [20]	$P < 0.002$		N: $N + \leq 3$; pT: T1, T2
Canylmaz et al. [47]	$P < 0.0001$	$P < 0.0001$	
Kim et al. [22]	$P < 0.001$		
Liang et al. [23]	$P < 0.001$		Stage: II, III a, III b
Schoenfeld et al. [48]	ns	ns	
Squires et al. [24]	$P = 0.05$	ns	
Stiekema et al. [41]	ns	ns	

ns not significant

margins [10, 12]. Only few authors reported good survival rates for R1 EGC patients who were not re-resected [49, 50]. Nagata found that approximately 70% of EGC patients with histologically positive margins (R1) did not develop recurrence [18]. In case of more advanced tumors, although RLI was generally recognized as a significant risk factor at univariable analysis in surgical studies, it sometimes lost significance in multivariable analyses (Table 4). Moreover, some authors reported that a further

intraoperative resection after a positive frozen section did not always change patient's prognosis. In detail, Squires et al., considering R0 patients submitted immediately to a new resection after a positive frozen section, observed an improvement in the local recurrence rate but the same poor outcome of R1 RLI patients [24]. Bissolati et al. also reported an unfavorable outcome for 35 patients even after re-operation [26]. Conversely, only one study showed a better outcome in this patient subset [19].

Indications for re-resection in early gastric cancer

The studies in which residual cancer was found in surgical specimen of patients previously treated with not radical endoscopic resection are reported in Table 5. The frequency of the residual cancer varied between 6.7 and 84% in relation to the characteristics of margin involvement after endoscopic resection.

The low incidence of residual tumor found in patients with only partial lateral margin involvement and no other risk factors for lymph node metastases led endoscopists

to manage these patients with close follow-up strategy performing endoscopic re-resection if new lesions were detected (Table 6). Relapse in this subgroup varied between 14% [8] and 36% [60].

A surgical resection was generally proposed in patients with massive lateral margin involvement, i.e., > 6 mm, or with lesions > 2 cm [60], in those with lateral margin involvement > 1 cm [58], or when vertical margins were involved (Table 7) because of the high incidence of residual disease and the risk of lymph node metastases.

Indications for re-treatment in previously surgically treated early gastric cancer are shown in Table 8. Surgeons

Table 5 Incidence of residual cancer on surgical specimen in endoscopically resected patients with RLI

References	No. of patients	No. RLI patients	No. retreated patients	Residual cancer after surgery
Nagano et al. [51]	726	319	31	22
Chung et al. [52]	19	19	19	11 (58%)
Oda et al. [53]	298	72+25	163	22 (13.5%)
Song et al. [54]	86	44	44	32
Lee et al. [55]	na	28	28	7
Jung et al. [56]	1743	118	118	29 (24.5%)
Kikuchi et al. [57]	1458	33 (LM+)	21 (63%) 13 by surgery, 8 by ESD	5/8 treated by ESD
Yoon et al. [58]	1012	102	46	17
Hoteya et al. [59]	2042	53	26 (49%)	10 (38.4%)
Kim et al. [60]	1083	55 (LM+)	0	Retreated if recurrence at follow-up
Noh et al. [61]	1064	21	10	6 lymph node metastases
Numata et al. [8]	1053	21	0	3 relapsed during follow up (endoscopically treated)

na not available

Table 6 Lateral margin involvement after endoscopic resection

References	No. of patients with positive lateral margin	Action taken			Notes
		Follow-up	Endoscopic resection	Surgical resection	
Nagano et al. [51]	309	288	–	21	18 (86%) microscopic residual cancer
Chung et al. [52]	9 (+ 6 ^a)	–	–	9 (+ 6 ^a)	EMR resection
Oda et al. [53]	72	41	12	19	12/53 non surgical patients with local recurrence
Lee et al. [55]	8 (+ 6 ^a)	0	0	8 (+ 6 ^a)	2/8 (25%) residual cancer in surgical specimen
Jung et al. [56]	26	–	–	26	13 (50%) residual cancer in surgical specimen
Kikuchi et al. [57]	33	12	8	13	No recurrence if ESD successful
Yoon et al. [58]	54 (+ 8 ^a)	NV	NV	NV	17/56 (30.3%) recurrence during close follow-up
Hoteya et al. [59]	53	27	11	15	34% residual or recurrent disease after retreatment or follow-up
Kim et al. [60]	55	55	–	–	Endoscopic treatment in the event of disease recurrence during follow-up
Numata et al. [8]	21	21	–	–	All local recurrence treated by additional ESD

^aLateral and vertical involvement

Table 7 Vertical margin involvement after endoscopic resection

References	No. of patients with positive vertical margin	Action taken			Notes
		Follow-up	Endoscopic resection	Surgical resection	
Nagano et al. [51].	10	–	–	10	4 (40%) microscopic residual cancer
Chung et al. [52]	4 (+ 6 ^a)	–	–	4 (+ 6 ^a)	EMR resection
Oda et al. [53]	25	na	na	17	–
Lee et al. [55]	3 (+ 6 ^a)	0	0	3 (+ 6 ^a)	1/3 residual cancer in surgical specimen
Jung et al. [56]	92	–	–	92	16 (17%) residual cancer in surgical specimen
Yoon et al. [58]	40 (+ 8 ^a)	NA	NA	NV	17/56 (30.3%) recurrence in close follow-up
Noh et al. [61]	21	11	0	10	No residual cancer in gastric wall but lymph node metastases in 7(15%)

^aLateral and vertical involvement; na, not available

Table 8 Indications for surgical treatment in T1 RLI

References	No. of patients	Positive	Suggested treatment	Note
Kim et al. [12]	8	1	Reoperation if < 5 LN +	If D2–3 gastrectomy was performed
Morgagni et al. [48]	648	11	Possibility of considering reoperation	5-year survival: 100%
Cho et al. [2]	2740	2	Reoperation if N0	If D2–3 gastrectomy was performed
Sun et al. [16]	341	5	Considered benefit of reoperation in early stages	If D2–3 gastrectomy was performed
Wang et al. [17]	341	1	Unknown	N+ determined worse outcome in positive margin patients
Nagata et al. [18]	410	10	Reoperation	Positive margins in deep sites and in multiple layers had poorer survival
Bickenbach et al. [20]	574	2	Unknown	Independent predictor of survival in T1–2 patients
Kim et al. [29]	2081	5	Reoperation	Gross distance > 1 mm was adequate to obtain microscopic negative margins

frequently advised re-operation but few authors reported data on re-resected patients.

Indications for re-resection in cases of locally advanced gastric cancer with RLI

In case of locally advanced gastric cancer with RLI, when a radical resection is achievable through a new surgical treatment, the indication for re-operation is generally evaluated on the basis of nodal stage (Table 9). However, it is not clear how surgeons identified radically re-resected patients given that none reported information on peritoneal cytology status and only in very few series an adequate lymphadenectomy was performed. Cascinu et al. proposed to re-resect node negative patients, but all the patients in their study were submitted to D1 lymphatic dissection [11]. Such limited dissection could not provide adequate information on nodal diffusion and on prognosis of patients. Kim et al. observed that microscopic RLI lost its prognostic impact

in multivariate analysis in all but in patients with less than five positive nodes disease when D2 or D3 lymphadenectomy was performed and thus hypothesized re-resection for such patients [12].

Squires et al. re-treated 48 RLI-positive patients, achieving an R0 resection [24]. This population showed a lower incidence of local relapse but similar survival of non-resected RLI patients. In 2015, Bissolati et al. also reported very low survival rates for 32 re-resected patients who showed a survival similar to that of not re-treated RLI advanced cancer [26].

RLI in mini-invasive surgery

Sarela et al. described a high incidence of margin infiltration (50%) in T3 cancer cases submitted to laparoscopic gastrectomy [62]. Nozaki et al. observed an RLI incidence of 9% after surgical wedge resection of EGC [63]. According to Nagata et al., the increasing use of the stapler will make

Table 9 Indications for surgical treatment in \geq T2 RLI

References	No. of patients	No. RLI	Treatment suggested	Note
Songun et al. [10]	699	41	Reoperation	Survival in patients with RLI was comparable with that of patients with positive cytology
Cascinu et al. [11]	237	22	Reoperation for N0 patients	In N0 patients, higher incidence of local relapse
Kim et al. [12]	619	46	Re-excision if 5 or less nodes positive	The significance of a positive margin was dependent on the extent of disease
Chan et al. [13]	137	25	Not suggested	Authors suggested frozen section assessment and 5 cm of clear macroscopic margins during gastrectomy
Mariette et al. [42]	94	8	Not suggested	In adenocarcinoma of the esophagogastric junction, transection must be performed at a distance of 8 cm from the tumor
Shen et al. [14]	191	16	Not suggested	In adenocarcinoma of the cardia, positive margins were an indication of advanced disease
Cho et al. [2]	2740	49	Reoperation in node-negative disease	All patients had undergone D2/D3 resection
Morgagni et al. [15]	2740	78	Reoperation only in T2 patients (6th TNM classification)	The impact of prognosis was independent of lymph node involvement in RLI patients
Sun et al. [16]	2728	110	Not suggested,	In D2/3 gastrectomy, patients with positive margins showed poorer outcome
Wang et al. [17]	1565	128	Not suggested	Positive lymph node metastasis determined the worst overall survival
Nagata et al. [18].	824	13	Reoperation or intensive follow-up	The status of the surgical margin could provide useful information for additional treatments
Chen et al. [46]	NA	122	Routine frozen section	Re-excision of a positive margin after frozen section improved prognosis, especially in <N2 patients and if D2 resection was performed
Zhang et al. [40]	142	16	–	T stage not specified. Proximal gastric carcinoma involving esophagus. Positive resection margins not significant for overall survival
Bickenbach et al. [20]	2384	106	Reoperation in <3 positive nodes and early T stage	Positive margins lost significance in patients with > 3 positive nodes or T3-4 disease
Liang et al. [23]	1025	75	Postoperative chemotherapy, reoperation only in early stage	Patients with positive margins had the same prognosis as those with stage IIIc
Schoenfeld et al. [48]	91	18	Chemotherapy	All patients underwent radiotherapy. Neoadjuvant chemoradiotherapy was recommended in high-risk patients
Stiekema et al. [41]	110	30	Chemoradiotherapy	R1 did not influence prognosis in patients who had chemoradiotherapy after surgery
Woo et al. [25]	1536	35	Reoperation	Locoregional recurrence was higher in the negative margin group All patients were stage III-IV
Bissolati et al. [26]	674	145	Frozen section in high-risk patients	For intestinal pattern cancers T4, EGJ location, less than 3 cm margin distance For T2–T4 diffuse/mixed pattern cancers, lymphatic infiltration, tumor diameter greater than 4 cm, EGJ location and serosa invasion

it harder to identify the correct margin, creating even more problems in this already complex area [18].

Recurrence in non re-resected RLI patients

In patients with RLI that did not receive additional resection, only 20–30% of recurrences involved local sites and anastomosis (Table 10). In Woo et al.'s study on 1536 patients, local recurrence was more frequent in the negative margin group than in patients with RLI (27.1 vs. 14.3%)

Table 10 Sites of recurrence

References	Recurrence (%)	Only locoregional recurrence (anastomotic) (%)	Locoregional recurrence plus other sites of recurrence (%)	Only peritoneal recurrence (%)	Only distant metastasis (%)	Multiple sites of recurrence (without locoregional involvement) (%)	Conclusion/comparison to R0
Mariette et al. [42]		0					RLI not correlated with anastomotic recurrence
Sun et al. [16]	64.5	29.6	29.6	21.1	14.1	5.6	Locoregional recurrence R1 > R0. Overall recurrence R1 > R0 in T1-2
Wang et al. [17]		9.5	3.5	23.3	20.6	15.1	
Bickenbach et al. [20]	76	23		32			
Squires et al. [24]		32					Local recurrence > R1 (univariate $P=0.01$; multivariate: ns) Hematogenous and peritoneal recurrence not associated with margin status
Stiekema et al. [41]	70	24	20	33	19	5	ns
Woo et al. [25]	63	4.8	9.6	28.6	38.1	19.0	R1 > peritoneal and hematogenous recurrence

ns not significant

[25]. Overall, there was a higher incidence of distant and peritoneal metastases and metastatic relapse occurred earlier than local recurrence. Moreover, a high number of patients had associated metastases, thus precluding further treatment.

Indications for re-resection in cases of duodenal margin involvement

The indications for surgical re-resection in case of RLI that are reported above based on tumor stage are mainly focused on proximal margin infiltration. Indeed, in case of duodenal involvement the issue is even more challenging and only the surgeon who performed the first resection can decide whether a new resection is feasible [64]. When duodenal involvement is > 4 cm, radical treatment may not be possible [65]. Pancreaticoduodenectomy is rarely proposed to achieve radical resection. A meta-analysis of a small number of heterogeneous studies carried out by Roberts et al. in 2012 revealed higher post-operative morbidity when there was substantial duodenal involvement [66]. The authors found not possible the

identification of a subset of patients who could benefit from pancreaticoduodenectomy.

Is it advisable to extend lymphadenectomy in cases of surgical re-resection for RLI?

Achieving a more extended lymphadenectomy in all RLI patients may be technically demanding and increase the morbidity of patients because of scar tissue, adhesions and risk of bleeding. None of the examined studies reported detailed information on this point. Whilst a new resection and wide lymphadenectomy could theoretically reduce local recurrence, the question is whether local recurrence actually impacts on the prognosis of patients with RLI. Our search of the literature revealed that few patients showed isolated local recurrence (Table 10).

Table 11 Multimodal treatment

Reference	No. patients	Indication for chemoradiotherapy
Kim et al. [12]	47	No
Cho et al. [2]	43	Only chemotherapy
Song et al. [67]	13	Yes
Canyilmaz et al. [47]	30	Low impact
Shoenfeld et al. [48]	19	Low impact
Stiekema et al. [41]	80	Yes
NCCN American guidelines [37]	–	Yes

Can a multimodal treatment be proposed?

Regarding radiochemotherapy as treatment option for RLI, according to the National Comprehensive Cancer Network (NCCN) American guidelines [37], some conflicting data exist (Table 11). Stiekema et al. showed that 30 R1 patients with RLI only submitted to radiochemotherapy did not show a worse prognosis than the R0 group [41]. Conversely, Canyilmaz et al. [47] and Schoenfeld et al. [48], analyzing 30 and 19 positive margin patients, respectively, submitted to multimodal treatment, confirmed worse survival rates [48].

Conclusions

Management of patients with RLI after endoscopic or surgical treatment for gastric cancer is challenging. For endoscopically treated early gastric cancer RLI includes a specific subset of patients who frequently show good prognosis even when not re-resected. In case of early gastric cancer with RLI after surgery, surgically re-resection to achieve radicality is generally indicated, but some authors, considering good results also in not re-resected EGC, propose a new surgical resection only in patients without comorbidity.

In advanced gastric cancer, frozen sections must be performed not only when the distance from surgical margins is lower than that proposed by guidelines, but also when risk factors for RLI are present, e.g., non differentiated cancer, large tumor size or advanced T stage. Frozen sections can help to reduce the possibility of margin involvement but false negatives are sometimes observed and this technique cannot be relied upon to completely eliminate the problem. Indications for re-resection in advanced gastric cancer are limited to cases with very confined nodal involvement, namely those with less than five pathologically positive nodes.

Multimodal treatment such as additive radiochemotherapy may improve survival in these patients and should then be considered as alternative to surgery, especially if a re-resection is technically challenging.

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Compliance with ethical standards

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