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World Journal of Gastrointestinal Oncology (*World J Gastrointest Oncol*, *WJGO*, online ISSN 1948-5204, DOI: 10.4251) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

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Complexity of molecular alterations impacts pancreatic cancer prognosis

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Abstract

Individualized cancer treatment (e.g. targeted therapy) based on molecular alterations has emerged as an important strategy to improve the current standard-of-care chemotherapy. A large number of studies have demonstrated the importance of biomarkers not only in predicting prognosis but more importantly in predicting the response towards therapies. For example, amplification or mutation status of the two biomarkers HER2 (human epidermal growth factor 2) and BRCA (breast cancer) can be used to decide on a specific targeted therapy in breast cancer. However, no biomarkers with a similar clinical impact have been identified in pancreatic ductal adenocarcinoma. Although many genome-wide and proteome-based high-throughput studies have identified candidate genes or proteins as promising biomarkers, none of them were eventually transferred into the clinical setting. Notably, the most reliable markers for predicting prognosis are still the tumor stage and grade and biomarkers for therapy response remain undefined. One reason lies in the lack of systemic approaches to analyze the complexity of dominating cancer pathways and the impact of such signal complexity on prognosis and therapy response.

Key words: Pancreatic cancer; Diagnostic markers; Biomarkers; Targeted therapy; Prognosis; Pathways

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INVITED COMMENTARY ON HOT ARTICLES

In a recent seminal study, Breitkreutz *et al*[1] compared the complexity of core signaling pathways in a variety of tumor entities including pancreatic ductal adenocarcinoma (PDAC). Specifically, 14 different pathways specific for one type of cancer were extracted from the Kyoto Encyclopedia of Genes and Genomes (KEGG)[1-3]. In order to analyze the influence of such a pathway complexity on 5-year survival rates, a metrics for network complexity (node degree entropy) has been used to perform correlation analyses. Prostate cancer was excluded from this analysis due to its highly differentiated phenotype and slow growth. The remaining 13 types of cancer show a high correlation between the 5-year survival rate and the node degree entropy of the corresponding network (R^2 = 0.7), e.g. pancreatic cancer with the shortest 5-year survival rate (5.5%) has a high node degree entropy (H = 2.05) whereas thyroid cancer showing the highest 5-year survival rate (97.2%) has a low entropy (H = 1.48). The authors concluded that complex structured networks generally point to a worse survival rate than simple structured networks. Moreover, they suggest intensifying research on network metrics in the context of survival probabilities and other clinical observations. Indeed, pancreatic cancer is an aggressive cancer entity with a very

complicated cancer signaling network. Although previous genome-wide sequencing efforts have identified a complex network of 12 core signaling pathways influencing the aggressive behavior of pancreatic cancer, it is not known how these 12 core pathways are coordinated or whether there are central players by which the pathways can be interconnected[4]. Assuming that the central players serve as connective 'linkers' within complex signaling networks, application of existing knowledge from protein-protein interaction analysis would reduce the complexity of networks, and would therefore help to uncover central players. To this end, Breitkreutz *et al*[1] analyzed protein-protein interaction networks of the individual specific cancer pathways extracted from KEGG. As many biological networks are scale-free, network analysis would focus on nodes with a high impact. Because node impact is not just given by its network degree, but by its property to connect different nodes or sub-networks, the authors use the betweenness centrality measure for further analysis. The betweenness centrality of a node is the proportion of the shortest paths in the network that include the node. Accordingly, nodes with a high betweenness centrality can be considered as potential therapeutic targets. For each network, the three nodes with the highest betweenness centrality were identified. This analysis yielded three candidate genes for pancreatic cancer consisting of *KRAS*, *JAK1* and *RALBP1*.

The network analysis suggests that KRAS, JAK1 and RALBP1 play an important role in mediating signal cross talks between different pathways in PDAC. Indeed, nearly all PDAC harbor oncogenic *KRAS* mutations, and *KRAS* mutations can also be detected in chronic pancreatitis and various early cancer lesions, such as pancreatic intraepithelial neoplasia, acinar-ductal metaplasia or cystic lesions[5,6]. Therefore, it is not surprising that KRAS has been identified by such analysis. However, *KRAS* mutations are neither a reliable prognostic marker nor a predictive biomarker for therapy, in as much as clinical trials targeting the KRAS signaling pathway do not show encouraging results[7]. Nevertheless, patients without *KRAS* mutations show a favorable response to combination treatment with gemcitabine and erlotinib[8].

Mouse models of pancreatic cancer suggest that oncogenic *Kras* mutation, pancreas-specifically (starting during embryogenesis) expressed from its endogenous locus, initiates alone the development of invasive PDAC albeit at a low efficiency. A 'second hit' such as loss of a tumor suppressor or the initiation of inflammation is required to increase the rate of/accelerate malignant transformation[9,10]. These observations underscore the necessity of an interaction between the RAS pathway and other signaling pathways in driving the formation of malignant pancreatic tumors. In addition, they also imply that *KRAS* effectors are widely 'connected' and have a broad biological effect on tumor behavior. A downstream target of the Ras GTPase is RALBP1, the second protein identified by the protein-protein network analysis. The protein is involved in the cellular stress response and is over expressed in several cancers in which it protects transformed cells from apoptosis and mediates resistance to various drugs[11,12]. Indeed, RALBP1 has been considered as a prognostic biomarker in colorectal cancer and high expression of RALBP1 is associated with shortened overall survival and early relapse[13]. *In vitro* studies of RALBP1 inhibition demonstrate reduced tumor cell proliferation and enhanced apoptosis in non-small cell lung cancer cells[14]. Furthermore, RALBP1 was identified as a possible mediator of metastatic invasion in PDAC[15]. Whether RALBP1 may constitute a potential drug target or a prognostic biomarker in PDAC is unclear.

The third candidate gene is JAK1, which has previously been shown to have pro-tumorigenic effects. JAK1 plays an important role in transmitting inflammatory signals through nuclear factor-κB signaling into epithelial cells. In general, inflammation signaling extensively interacts with oncogenic KRAS signaling and promotes the development of PDAC[16,17]. However, the exact role of JAK1 in this context remains unknown. A clinical trial of a JAK1 inhibitor demonstrated that JAK1 may be a target for myelofibrosis because treatment reduced the level of inflammatory cytokines and improved systemic symptoms[18]. Hence, this data suggest that JAK1 inhibition affects inflammatory processes. Additionally, *in vitro* studies revealed decreased tumor cell proliferation and activated apoptosis of glioblastoma cells and multiple myeloma cells following JAK1 inhibition[19,20]. However, further investigation is necessary to uncover the potential link between KRAS and JAK1 as well as the potential of JAK1 as a prognostic marker or a drug able target in PDAC.

In conclusion, the study by Breitkreutz *et al*[1] reveals that KRAS, RALBP1 and JAK1 may constitute a biochemical network which coordinates the malignant behavior of cancer cells. Further analysis of this network may yield novel cancer biomarkers and therapy targets.

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REVIEW

Clinical importance and surgical decision-making regarding proximal resection margin for gastric cancer

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Abstract

Because of the intramural spread of gastric cancer, a sufficient length of a resection margin has to be attained to ensure complete excision of the tumor. There has been debate on an adequate length of proximal resection margin (PRM) and its related issues. Thus, the objective of this article is to review several studies on PRM and to summarize the current evidence on the subject. Although there is some discrepancy in the recommended values for PRM between authors, a PRM of more than 2-3 cm for early gastric cancer and 5-6 cm for advanced gastric cancer is thought to be acceptable. Once the margin is confirmed to be clear, however, the length of PRM measured in postoperative pathologic examination does not affect the patient's survival, even when it is shorter than the recommended values. Hence, the recommendations for PRM length should be applied only to intraoperative decision-making to prevent positive margins on the final pathology. Given that a negative resection margin is the ultimate goal of determining an adequate PRM, development and improvement of reliable methods to confirm a negative resection margin intraoperatively would minimize the extent of surgery and offer a better quality of life to more patients. In the same context, special attention has to be paid to patients who have advanced stage or diffuse-type gastric cancer, because they are more likely to have a positive margin. Therefore, a wider excision with intraoperative frozen section (IFS) examination of the resection margin is necessary. Despite all the attempts to avoid positive margins, there is still a certain rate of positive-margin cases. Since the negative impact of a positive margin on prognosis is mostly obvious in low N stage patients, aggressive further management, such as extensive re-operation, is required for these patients. In conclusion, every possible preoperative and intraoperative evaluation should be thoroughly carried out to identify in advance the patients with a high risk of having positive margins; these patients need careful management with a wider excision or an IFS examination to confirm a negative margin during surgery.

Key words: Resection margin; Proximal resection margin; Negative resection margin; Positive resection margin; Gastrectomy; Gastric cancer

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INTRODUCTION

Although there have been great improvements in the diagnosis and treatment of gastric cancer, it remains a major health problem as the fourth most common

cancer and the second leading cause of cancer death worldwide[1,2]. Complete resection with negative surgical margins along with lymph node dissection has been accepted as the only possibly curative treatment for gastric cancer. The gross resection margin should be somewhat far from the edge of the mass to avoid the possibility of cancer involvement at the line of resection, because tumor cells spread intramurally beyond the macroscopically detectable boundaries of the lesion. Surgeons are also concerned about the possibility of recurrences with a short distance between tumor mass and resection margins. Hence, they try to remove the tumor completely with a wide range of normal stomach.

The adequate length for the required resection margin to be obtained during gastrectomy has been debated, but it is important because it determines the extent of the operation. Although there have been several studies on the sufficient length of margins that guarantees tumor-free resection and prevents local recurrences[3-9], a definite consensus has not yet been reached, especially about the proximal resection margin (PRM). Furthermore, it is hard to secure the recommended length of PRM in some patients, and the appropriate management for these patients is still controversial.

The purpose of this article is to review issues and controversies about the importance of safe margins, an adequate length of PRM, and how to deal with the patients with insufficient PRM.

SIGNIFICANCE OF NEGATIVE RESECTION MARGIN

According to the criteria of the International Union against Cancer/American Joint Committee on Cancer, curative (R0) surgery is defined as *en bloc* resection of primary tumor and complete lymphadenectomy without microscopic or macroscopic residual disease[10]. Thus, a microscopically negative resection margin is a prerequisite for R0 resection. To clearly discuss margin status in this article, we defined the 'positive resection margins' as the presence of viable tumor cells at the line of resection on the postoperative pathologic examination even in gastrectomy with curative intent with or without an intraoperative frozen section examination. Furthermore, the term, 'unintended positive resection margin', was used in the case of tumor involvement at the resection margin on the final pathologic examination, although it was thought to be negative by an intraoperative frozen section examination (false negative). We also defined the 'negative resection margins' as the absence of both macroscopic and microscopic tumor involvement at the resection line confirmed by the final pathologic examination.

Not surprisingly, most studies have demonstrated that a positive margin is an independent unfavorable factor for patients who have had a gastrectomy[11-21]. In this section, the negative impact of a positive margin on tumor recurrence and patient survival was analyzed in detail.

Impact of positive resection margins on recurrences

Recurrence following curative surgery is a critical problem for patients with gastric cancer, because most patients die within the first year after diagnosis of recurrence and the mean survival time has been reported to be only 8.7 mo[22]. Since any residual tumor cells at the resection lines may contribute to a recurrence, it is not unexpected that patients with positive margins have more recurrences than those with negative margins[3,18,19]. In detailed analysis, however, there are several interesting issues.

First, recurrences do not always develop in all patients whose resection margins have remaining cancer cells on microscopic examination. This phenomenon can be partly explained by the successful eradication of these cells by postoperative adjuvant therapies which are performed in some patients with positive margins[5]. Furthermore, a few residual cancer cells could be eliminated by the patient's own immune system or poor blood supply at the resection margin[17,20]. Another possibility is that tumor cells are involved only in diagnostic resection margins but not in the true surgical margins. A discrepancy between diagnostic margins and true surgical margins due to the removal of the stapled resection lines before histological examination might lead to misinterpretation of margin status[20].

Second, locoregional recurrence is not always the most common type of relapse in positive-margin patients. Clinically, recurrences are classified as locoregional, peritoneal, or distant. A locoregional recurrence is defined as any cancer recurrence in the gastric bed, upper abdominal retroperitoneal lymph nodes or at the local anastomotic sites[18]. Of the three patterns of recurrence, the locoregional type seems to be the most affected by positive margins, in that residual tumor cells can grow and lead to a recurrence at that location. However, Wang *et al*[21] demonstrated that distant metastasis constituted the most common site of recurrence in positive-margin patients, whereas the rate of locoregional recurrence was the lowest. Considering that locoregional is reported to be the most common recurrence pattern in negative-margin patients[23,24], these results are very interesting, because negative margins resulted in more locoregional recurrences but positive margins resulted in more distant recurrences. Since positive-margin patients are likely to suffer from more aggressive cancer which frequently results in distant or peritoneal recurrences, they might have more distant or peritoneal recurrences than locoregional. Consequently, the aggressiveness of the cancer rather than margin status is what really affects the recurrence patterns in positive-margin patients. Nonetheless, another group showed somewhat different results, which suggested the possible contribution of residual tumor cells at a resection line to locoregional recurrence[18]. Hence, the relationship between positive margins and locoregional recurrence remains in dispute and further studies are needed.

Third, in one study that compared the recurrence patterns by pT, pN, and tumor-node-metastasis (TNM)

Table 1 Effects of positive margins on survival

Ref.	Inclusion	*n*	Effect of positive margins on survival		
			All patients *P* value	Subgroup analysis	
				Nodal status	*P* value
Kim *et al*[11]	GC	619	< 0.0001	≤ 5 LNI	0.0001
				> 5 LNI	NS
Cascinu *et al*[19]	AGC	259	Significant	Node negative	0.001
				Node positive	NS
Cho *et al*[16]	AGC	2740	0.0028	Node negative	0.0001
				Node positive	0.259
Sun *et al*[16]	GC	2728	< 0.001	N0	< 0.001
				N1	0.007
				N3, N4	NS
Morgagni *et al*[17]	GC	89	< 0.0001	N0	0.001
				N1	0.003
				N2	0.009
				N4	NS

GC: Gastric cancer; AGC: Advanced gastric cancer; NS: Not significant; LNI: Lymph node involvement.

stage, higher recurrence rates for positive-margin patients were seen only in pT1-2, pN0-1, and stage Ⅰ-Ⅱ cancer[18]. In other words, the margin status did not affect recurrence rates in the patients with T3-4, N2-3, and stage Ⅲ-Ⅳ cancer. The effects of a positive margin seem to be masked by the aggressiveness of the cancer, which is thought to have a strong influence on recurrences in advanced-stage patients. Thus, these patients might not benefit from negative resection margins, although every effort to make margins clean should still be made for curative surgery[25].

Impact of positive resection margins on survival

In the registry study by the American College of Surgeons, the 5-year survival rate of the patients with microscopically clear margins was 35% and 13% in those with positive margins[26]. Poorer survival of positive-margin patients was also reported by others[27-29]. As summarized in Table 1, many studies have demonstrated the negative predictive value of positive margins on survival. *P*-values for this association were always significant for the entire population. In subgroup analysis, however, positive margins were associated with poor survival only in the patients with low N stage gastric cancer[11,16-18]. The association was not significant for those who had many tumor-involved lymph nodes, possibly because the adverse effects of positive margins might be overwhelmed by the more detrimental impact of nodal metastasis on survival.

A similar tendency was seen after stratifying T stage. The negative impact of positive margins was limited to T1-2 stage patients[18]. Accordingly, this seems to impact patients with either low N stage or low T stage[30]. On the contrary, some authors reported discordant results with regard to T1 or early gastric cancer (EGC)[5,17,31]. Since EGC patients with positive margins had a good survival rate in their studies, they argued that a positive margin was not a significant adverse factor for EGC patients. Their good survival was explained by limitation of laterally spreading T1 cancer along the resection line which lacked a good blood supply[17]. Putting all this together, the negative predictive value of positive margins is prominent in lower T stage disease, while it is still controversial in EGC (T1) patients.

Furthermore, when it comes to overall TNM stage, the predictive value of positive margins is less clear. This is because some have concluded that the margin involvement leads to poorer survival only in patients with overall stage Ⅰ and Ⅱ cancer[18,32], whereas others have described different results[17,21].

In conclusion, although margin status is an important prognostic factor for survival after gastrectomy, subgroup analyses revealed that this effect was restricted to early stage patients, especially those with minimal or no nodal involvement. Therefore, it is reasonable to consider the stage of cancer in predicting survival of patients with positive margins and plan further management for them. For example, positive margins in N0-N1 patients should be regarded as a more serious condition which needs aggressive retreatment. Furthermore, if N0-N1 stage is suspected before or during surgery, it would be better to avoid positive margins at all costs, including using a wide excision and an intraoperative frozen section (IFS) examination of margins.

Predictors of positive resection margins

Many predictors of positive margins after curative resection of gastric cancer have been elucidated. Larger tumor size, higher T stage, higher N stage, higher overall stage, Borrmann type 4, diffuse histologic type, positive lymphatic vessel invasion, and upper tumor location were found to be associated with a higher probability of resection line infiltration by tumor cells[11,16-19,21]. On multivariate analysis, higher T stage, higher N stage, larger tumor size, and diffuse histologic type were significant independent predictors for a positive margin[16-18,21]. Surgeons should be more cautious about margin involvement when treating patients with these characteristics. Thus, thorough preoperative evaluations by an endoscopist, radiologist and pathologist are needed to determine the properties of the cancer and predict the risk of the patient having positive margins. Additionally, an IFS examination is also recommended for these high risk patients to prevent positive margins; this will be discussed later in this article. These preoperative and postoperative efforts are important as they have reduced the rates of positive margins in Japan[33].

ISSUES REGARDING PROXIMAL RESECTION MARGIN

Why is the proximal resection margin a problem?

Surgeons try to remove gastric cancer completely with negative resection margins to reduce the risk of recurrences, which can result from even a few residual cells. For a gastrectomy to be curative, a sufficient distance

Table 2 Studies on an adequate length of proximal resection margin in gastric cancer

Ref.	Characteristics	RLPRM	Brief results of the study
Bozzetti *et al*[4]	without SI	⩾ 3 cm	No positive margin if gross PRM ⩾ 3 cm
	with SI	⩾ 6 cm	No positive margin if gross PRM ⩾ 6 cm
			(0% if PRM ⩾ 6 cm *vs* 7% if PRM < 6 cm)
Ito *et al*[7]	Cardia		
	T1, T2	⩾ 4 cm	No positive margin if gross PRM ⩾ 4 cm
	T3, T4	⩾ 6 cm	No positive margin if gross PRM ⩾ 6 cm
Papachristou *et al*[3]	Gastric cancer	⩾ 6.5 cm	Median length of gross PRM in patients with or without recurrences: 6.5 cm *vs* 3.5 cm, respectively
Kim *et al*[36]	Upper third	⩾ 2 cm	Recurrences: 8.2% (PRM > 2 cm) *vs* 14.5% (1-2 cm) and 30% (< 1 cm), $P = 0.024$
Ha *et al*[6]	EGC	-	PRM did not affect survival if margins were negative
	AGC	⩾ 3 cm	Recurrences: 32.9% (PRM ⩾ 3 cm) *vs* 37.6% (< 3 cm), NS;
			5-yr survival: 57% (PRM ⩾ 3 cm) *vs* 46% (< 3 cm), $P = 0.02$

RLPRM: Recommended length of proximal resection margin; PRM: Proximal resection margin; SI: Serosa infiltration; NS: Not significant; EGC: Early gastric cancer; AGC: Advanced gastric cancer.

from the gross lesion to any surgical margin is necessary because of the following reasons. First, a grossly normal resection margin, determined by intraoperative inspection or palpation, is often insufficient to ensure pathologic clearance due to intramural spread of gastric cancer. Second, surgeons are concerned about the high probability of recurrence if the distance between the tumor and resection margin is short. Hence, complete resection of the tumor mass with a wide margin of normal stomach is required. There have been a number of studies and recommendations on the sufficient length of proximal and distal resection margins (PRM and DRM, respectively), which aimed to guarantee negative margins on final pathologic examination and to prevent recurrences after gastrectomy[3-7,34,35]. These references can help surgeons to decide the extent of surgery in the operative field by making them confident of negative margins whenever following the recommendations.

DRM has been generally determined as at least 2 to 4 cm distal to the pylorus[5,8,9]. More debate on an adequate length of DRM is meaningless, because it must be proximal to the orifice of the common bile duct and pancreatic duct no matter how long a DRM we want to secure. If a tumor requires a longer DRM that includes the orifice, it is likely to be metastatic disease and the surgical option needed is no longer gastrectomy alone.

On the other hand, the adequate length of PRM is more variable and there is still inconsistency in specific recommended values between authors[3-7]. To what extent the grossly normal stomach tissue needs to be excised proximally is important, because this is critical in deciding the type of resection. For example, for a tumor located in the middle part of the stomach, the length of PRM that surgeons try to achieve determines whether a total gastrectomy (TG) or distal gastrectomy (DG) should be performed. In addition, the recommendations regarding the way to manage the patient who has a shorter PRM postoperatively than was originally intended during surgery is another important issue. In this section, we will introduce several studies about PRM and discuss the related problems.

Studies on the adequate length of proximal resection margin

Table 2 is a summary of various studies that have suggested an adequate length of PRM for a gastrectomy. Authors recommended such values either to ensure negative margins on final pathologic exam or to prevent recurrences which were thought to be a result of insufficient distance between gross resection margin and the lesion. Bozzetti *et al*[4] and Ito *et al*[7] documented that there were no positive-margin cases if gross PRM was longer than certain figures, and they recommended them as adequate lengths of PRM for negative margins. Other authors have compared the rate of recurrences and survival according to the length of PRM and suggested proper cut-off values that provided a significantly low rate of poor outcomes[3,6,36].

Recent guidelines from the Japanese Gastric Cancer Association[35] recommended 2 cm or more gross PRM for T1 gastric cancer, 3 cm or more gross PRM for T2 or deeper tumors with an expansive growth pattern, and 5 cm or more gross PRM for T2 or deeper tumors with an infiltrative pattern. When these rules cannot be observed, the guidelines advised to examine the PRM by IFS.

Although the values for each situation were somewhat different between the studies, similarities were also found. First, a longer PRM was needed for more advanced or aggressive cancer. Three to six centimeters of gross PRM for advanced or aggressive gastric cancer was generally recommended, while 2-3 cm of PRM was adequate for EGC. Second, recommended lengths differed by the characteristics of the tumor, such as T stage, histologic type, and location. An infiltrative type of gastric cancer requires a longer PRM.

Determining an adequate length of proximal resection margin: How long is safe?

One of the most important reasons for the efforts to determine an adequate length of PRM and to try to achieve it during surgery is to obtain negative resection margins in all cases. An adequate length of PRM, however, is emphasized not only to ensure negative

margins. Many surgeons are anxious about a short PRM, even when it is confirmed to be negative in the final pathologic exam. This is because a short PRM has been associated with more recurrences and poorer survival. The median length of gross PRM in patients with recurrences was found to be 3.5 cm *vs* 6.5 cm in patients who did not develop recurrences[3]. Kim *et al*[36] documented that a PRM shorter than 2 cm resulted in a higher rate of recurrences in patients with upper gastric cancer. Furthermore, the survival rate of AGC patients was lower if PRM was less than 3 cm in the final pathological examination[6]. According to these studies, a short PRM itself seemed to negatively affect the patient's outcome. Nevertheless, we have to be careful about the interpretation of these findings for two reasons. First, the PRM tended to be short in patients with advanced stage cancers in which poor prognosis was expected. This means the aggressiveness of the cancer in cases with a short PRM could be the real cause of a poor outcome, and thereby could serve as a confounding factor when assessing the correlation between a short PRM and adverse outcome. Second, the group of patients who had inadequate PRM included positive-margin cases. Poorer outcomes seen in that group might be partially attributed to these positive-margin patients. Therefore, it has been hard to know the pure effect of the length of PRM on prognosis.

Recently, some authors have found that the length of PRM measured by final pathology did not affect the 5-year survival rates if a negative margin was obtained[37,38]. These results could, to some degree, answer the question about the true impact of PRM length on prognosis. Based on these studies, the belief that short PRM would result in more recurrences and poorer survival has to be reconsidered. It also seems that the length of PRM is irrelevant if resection lines are clear on final pathology, and the concept of an adequate length of PRM should be applied to the intraoperative determination of a gross resection margin but not to the postoperative pathologic assessment.

The fundamental problem here is that no reliable method has been available thus far to ensure negative margins in the operating room, except resecting the tumor mass with a wide range of normal stomach. Therefore, current recommendations for gross PRM are still significant and any intraoperative decision about the extent of surgery has to be made in accordance with them. In some cases in which the recommended length of PRM cannot be attained during surgery, IFS examination is helpful to ensure negative margins.

IFS examination of PRM

IFS examination of resection lines is commonly used to assess margin status. The accuracy of this procedure has been reported to be about 98%[39] and both sensitivity and specificity are seen to be high[40]. Some authors have encouraged the routine use of IFS examination[30,34]. Nonetheless, it is more practical to selectively perform this procedure in patients who may benefit from it, since it is costly, time-consuming, and not always available[41].

The most suitable candidates for IFS examination are those who have a high possibility of having positive margins, including patients with T3-T4 stage, poorly differentiated, Bormann type Ⅳ or signet ring cell type gastric cancers[42-44]. When the gross margin status is still suspicious despite acquisition of the recommended length of PRM, IFS examination will help to avoid positive margins. This technique is also used to determine the extent of surgery, providing negative margins when it is impossible to attain the recommended length of PRM. Even in this case, however, all attempts must firstly be made to achieve the recommended length of PRM, because IFS exam may give false-negative results[27,45]. An unintended positive margin, defined herein as a false-negative result of IFS exam, has been more frequently associated with signet ring cell or poorly differentiated type gastric cancers due to their extension under the submucosal layer of the gastric wall[46]. Of course, patients with unintended positive margins are also included in the positive-margin cases and need to be treated as such. Fortunately, the numbers are expected to decrease by virtue of several improvements in this procedure, such as cytokeratin immunohistochemistry[47].

Inadequate proximal resection margin and re-operation

Although surgeons have done their best to perform tumor-free resection based on the present recommendations, the prevalence of positive margins has been reported to be 0.8%-20.0%[11,19,26,29,42,48]. Also, the distance to resection margins measured intraoperatively sometimes differs from values measured in the final pathologic exams. For these reasons, the way to manage the patients with an insufficient length of PRM or a positive margin is an important issue. Do we have to re-operate these patients to provide adequate margins?

Studies have shown that if PRM is confirmed to be negative for malignancy but shorter than the recommended length, further resection to acquire a longer PRM is unnecessary, since better survival cannot be expected[37,38].

Regarding the positive-margin cases, the necessity of re-operation depends on whether the patients will benefit from it or not. The benefits of reoperation always have to be balanced with the risks of this technically demanding procedure. In the previously mentioned studies, a negative margin improved the survival of patients with early stage cancer[16,19,30]. Hence, an extended re-operation appears to have the most obvious survival advantage in low-stage patients, especially when few nodes are involved (N0 or N1). In contrast, as advanced N stage patients with positive margins might not benefit from an extended re-excision, the decision has to be made with much deliberation. In fact, multidisciplinary options including chemotherapy and irradiation are more appropriate treatments for positive-margin patients[16,49]. Even with all options, however, the most important objective should be to prevent positive margins beforehand, by

evaluating the cancer status before and during surgery to determine the patients with a high risk of having positive margins and treating them more carefully.

Optimal type of gastrectomy and the length of proximal resection margin

Different types of gastrectomy have been recommended for gastric cancers located in each part of the stomach. For proximally located gastric cancers, TG has been recommended as a first choice, excluding limited cases in which some authors have suggested proximal gastrectomy as an alternative[7,36,50]. DG is generally performed for gastric cancers of the lower third of the stomach, since DG showed a similar long-term prognosis, improved quality of life and lower morbidity for distal-third cancer in randomized prospective studies[51,52].

When it comes to middle-third gastric cancers, the most appropriate procedure is controversial because of the ambiguity of their location. The issues surrounding adequate PRM greatly matter for these, because the choice between TG and DG depends on the length of PRM required. Generally, a longer PRM can be achieved by TG, whereas DG is associated with a better quality of life and similar or lower morbidity[51-55]. Of the two options, TG has been adopted as the standard treatment for middle-third gastric cancer by many surgeons who are concerned about the possibility of recurrences with a short PRM after DG. As explained above, however, the length of PRM does not impact prognosis if the lines of resection are free of tumor[37,38]. In these studies, the authors suggested DG should be the first surgical option for intermediately located gastric cancer if negative margins could be guaranteed. Furthermore, when the surgery has to be converted from DG to TG to gain a few more centimeters of PRM to obtain the recommended values, DG with IFS examination, which can provide better quality of life, is a better choice if negative margins are confirmed by the frozen exam. When doing this, there is a practical problem that the residual part of the stomach can become necrotic owing to the poor blood supply. Therefore, surgeons try to preserve a short gastric artery technically as much as possible to make it successful.

In addition, we expect that less extensive surgery can be performed more commonly in gastric cancer patients who are not eligible for DG based on the current recommendations on PRM length, if unintended positive margins can be prevented by improvement of IFS exam or if other reliable methods to confirm negative margins intraoperatively are developed.

CONCLUSION

Since tumor infiltration at resection lines has been accepted as an adverse prognostic factor, negative resection margins are crucial components of curative surgery, which is the only currently available method offering a cure for gastric cancer. To ensure negative margins in the final pathologic exam, a sufficient length of gross PRM is always required. Whenever surgeons try to attain 2-3 cm of gross PRM in EGC and 3-5 cm of gross PRM in AGC during the operation, positive margins should be avoided. If the final PRM examination is clear but shorter than that originally intended intraoperatively, a short PRM itself seems not to affect a patient's prognosis. Along with this principle, IFS examination of resection lines is also used to confirm margin status in various situations. If despite all attempts, however, there are still positive margins, then re-operation is reasonable, especially in those who have low N stage diseases. In conclusion, achieving a negative resection margin is the ultimate goal when determining the adequate length for PRM and debating related issues. Every possible preoperative and intraoperative evaluation should be thoroughly carried out to find the patients with a high risk of having positive margins in advance, and subsequent careful management of these patients with a wider excision or an IFS examination to confirm a negative margin during surgery is necessary.

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Acknowledgments

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5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

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Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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