

Review

Extent of Surgical Resection for Gastric Cancer: The Safety Distance Between the Tumor and the Proximal Resection Margin

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Abstract. A potentially curative treatment scheme for gastric cancer is considered futile without a proper surgical resection. An oncological, surgical resection for gastric cancer prerequisites a proper resection of the stomach, and a D2 lymph node dissection followed by reconstruction of the gastrointestinal tract continuity. Recently, as the favorable impact of organ preserving surgery on functional outcomes has been increasingly appreciated; distal gastrectomy represents a valid alternative to total gastrectomy provided that the proper oncological principles are not violated. However, the appropriateness of distal gastrectomy as a valid type of resection becomes synonymous with achieving a negative proximal resection margin. The purpose of the present study was to assess the optimal distance between the tumor and the resection margin in a gastrectomy with curative intent, performed for gastric cancer, by reviewing the relevant literature. Having in mind, the well documented discrepancy between the gross and the pathologic boundaries of the tumor, pitfalls might be encountered. Current published guidelines have used a “safety distance” i.e., >4 or 5 cm between the proximal macroscopic tumor

border and the proximal resection margin in order to guarantee a negative resection margin on pathology. An increased distance of safety is currently proposed in high-risk tumors such as tumors of the diffuse histological type.

According to the GLOBOCAN 2018 data, gastric cancer is the fifth most frequent cancer, and the third cause of cancer-related deaths globally (1). In general, gastric cancer prognosis remains poor (2). Depending on stage, the 5-year survival rates for patients treated with curative intent falls from 70% for stage I patients to less than 30% for gastric cancer patients of more advanced disease stages (3). It is an indisputable fact though, that significant progress in the treatment of gastric cancer has been made during recent decades. Multimodal therapeutic approaches combining radiotherapy, chemotherapy either in the neo-adjuvant or adjuvant setting, and, ultimately, surgery have offered improved outcomes (4).

However, a potentially curative treatment scheme for gastric cancer is considered futile without a proper surgical resection (5). In regard to the surgical treatment of gastric cancer, several areas have become the field of constant debate, within the surgical community, with the proper extent of lymphadenectomy being the most notable. More specifically, in Eastern countries D2 lymphadenectomy has been traditionally considered the standard procedure for gastric cancer on the basis of its associated superior survival and recurrence results (6). On the contrary, a more limited lymph node dissection approach had been initially adopted in respective Western Institutions as initial reports attributed to the extended lymphadenectomies increased the rate of surgical complications and higher peri-operative mortality, without a real survival benefit. The incorporation, however, of more recent evidence directly challenged this approach and established D2 lymph node dissection as the standard of care in Western Institutions, as well (7).

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Apart from lymphadenectomy, the resection of the stomach along with the primary tumor, either in the form of a total or a distal gastrectomy, is an integral part of the surgical treatment. However, patients submitted to gastric resection for cancer are deprived, either in total or in part, depending on the type of gastrectomy of an organ *i.e.*, stomach with significant physiological function as a part of the alimentary tract. Recent literature reports underline that the extent of gastrectomy influences negatively the quality of life and the nutritional status of patients after gastric cancer surgery (8, 9). Furthermore, the incidence of well-defined postgastrectomy complications and symptoms such as reflux and dumping syndrome seems to be limited, should an approach of organ sparing resection is followed (10). Within this framework, organ-preserving surgery appears as the ideal scenario provided that the proper oncological principles are not violated.

In general, the appropriateness of distal gastrectomy, as an oncologically correct resection type, becomes synonymous with achieving a negative proximal resection margin on pathology. The purpose of the present study was to assess the optimal distance of safety between the gross gastric tumor border and the proximal resection margin, during a distal gastrectomy with curative intent, in order to achieve oncological adequacy by reviewing the relevant literature.

Gross and Histologic Classification of Gastric Cancer

The gross appearance of gastric cancer, on endoscopy, can be exophytic, ulcerated, infiltrative or combined. Based on the classic, Borrmann's classification, the gross appearance of gastric cancers can be divided into four distinct types: Type I refers to gastric cancer with polypoid growth, type II to fungating growth, type III to ulcerating growth, and type IV to gastric cancers with diffusely infiltrating growth pattern. The latter type is also referred to as linitis plastica, a condition where the gastric wall is, almost in total, involved by infiltrating tumor cells (11).

In regard to histology, gastric cancer demonstrates notable heterogeneity at both architectural and cytologic level. The Lauren's classification made up the basis for the histologic classification of gastric cancer. According to this classification, the two major subtypes of gastric cancer are the intestinal and the diffuse type adenocarcinoma, accounting for more than 85% of all gastric cancers. An indeterminate type was additionally proposed to include gastric cancers without distinct histological characteristics (12).

Technical Considerations

An oncological, surgical resection for gastric cancer prerequisites a proper resection of the stomach, and a D2

lymph node dissection followed by reconstruction of the gastrointestinal tract continuity. In regard to the gastrectomy itself, with the exception of locally advanced gastric cancer, where multivisceral resections might be required, the distal resection margin is by definition pre-specified. The first part of the duodenum, usually a level 1 to 2 cm from the pylorus, has been routinely used as the distal resection margin irrespective of the location of the primary tumor within the stomach. The same principles apply for the proximal resection margin, when a total gastrectomy is the procedure of choice, usually for tumors of the upper and middle third of the stomach. In this case, the gastroesophageal junction is the pre-specified proximal resection margin.

In the past, total gastrectomy was considered as a standard type of gastrectomy in all gastric cancer patients because it could safely guarantee, in the most efficient way, pathologically clear proximal resection margins (13). However, there were no significant differences in the survival rates and complications between distal and total gastrectomy in patients with gastric cancer in the distal third of the stomach (14). Within this context, taking advantage of the favorable functional outcomes of organ preserving surgery, in the form of distal gastrectomy, appears as a totally justified approach as long as the basic oncological principles are not violated. In regard to the latter, a clear proximal resection margin on pathology is the condition that could objectively permit the preservation of the upper part of the stomach.

Proximal Resection Margin

A pathologically clear proximal resection margin is one of the most important elements of a gastric cancer resection with curative intent. With the exception of total gastrectomy, with the predefined proximal resection margin *i.e.*, at the level of gastroesophageal junction, distal gastrectomy prerequisites elaborative surgical decision making in regard to defining the level of proximal transection of stomach. The problem is that there is often a discrepancy between the gross/macrosopic assessment of the tumor borders as assessed by the involved surgeon and the actual proximal margin status as assessed during the pathological examination of the surgical specimen.

Aiming to overcome this obstacle in the quest for R0 proximal resection margins, a "safety" distance from what the involved surgeon assesses as the most proximal tumor border to the proximal resection margin has been suggested. Several studies have tried to define this distance of safety. A retrospective study by Bozzetti *et al.*, assessing 343 gastric cancer patients, showed that none of the patients with a proximal safety margin of more than 6 cm had infiltrated resection margins. In addition, the authors highlighted serosal involvement as a risk factor for positive proximal resection margins and suggested that for primary tumors, not

extending to the gastric wall serosa, a decreased distance of safety *i.e.*, 3 cm appears justified (15).

The importance of the T stage of the tumor on the resection margin status has been further highlighted by Kim *et al.* in their report, evaluating 2,081 patients with early gastric cancer who underwent gastrectomy. In this study, a margin of more than 1 mm proved safe in this early gastric cancer patient group (16). In 2015, a multicenter study out of seven Institutions of the U.S. Gastric Cancer Collaborative aimed to assess the prognostic value of proximal margin distance on survival outcomes after distal gastrectomy. The authors concluded that the prognostic value of proximal margin distance after distal gastrectomies for gastric cancer appears to be stage specific. More specifically, in stage I, a 3 to 5 cm proximal margin is associated with the same improved overall survival as a margin of more than 5 cm. On the other hand, in patients of more advanced disease stage (II-III), other adverse pathological factors more strongly impact survival than proximal margin distance (17).

In a similar fashion, Berlth *et al.* highlighted the diffuse histology as a risk factor for underestimation of proximal margin length and suggested that a margin of more than 3 cm combined with frozen margin confirmation can be considered safe (18). This latter study aimed to answer, as well, whether a decreased proximal margin length can have a detrimental effect on survival or locoregional recurrence after distal gastrectomy. The results showed that proximal margin length does not affect outcomes after distal gastrectomy for gastric cancer. Aiming to provide answers to the same question Lee *et al.* and Jang *et al.* showed that provided that the condition of pathologically clear resection margins is fulfilled, the length of the negative resection margin did not affect long term outcomes *i.e.*, survival and recurrences after distal gastrectomy for gastric cancer (19, 20).

It becomes obvious that the important determinant in gastric cancer prognosis is the microscopic status of the resection margin and not the length of the negative margin. The length itself has been utilized as a “safety valve” guaranteeing an R0 resection. Intraoperative frozen section analysis, despite its limitations, might be an invaluable adjunct in this direction especially in cases of high risk for atypical growth tumors. The diffuse type and tumors of advanced T stage fall into this high risk for misidentification of the tumor borders category. A recent study by Hayami *et al.* aimed to evaluate the degree of discrepancy between the macroscopic and pathological borders of gastric cancer in 1,494 gastric cancer patients. According to this study, in T1 tumors the maximum discrepancy was 20mm for well or moderately differentiated adenocarcinomas and 40mm for poorly differentiated adenocarcinomas and signet ring carcinomas. In patients of more advanced T stage *i.e.*, T2–4, the maximum discrepancy was 30 mm in tumors with expansive growth pattern.

Interestingly, the maximum discrepancy for tumors of the infiltrative growth type was 60 mm (21).

Current Guidelines

Different scientific communities have published guidelines on the optimal proximal to tumor macroscopic-free margin in order to assure pathological clear proximal resection margins, incorporating all the existing knowledge on the field. However, there is indeed a notable heterogeneity in the recommendations. The National Comprehensive Cancer Network (NCCN), in its 2019 guidelines, recommends a minimum resection margin of 4 cm from the primary tumor for all resectable T1b–T3 gastric tumors while multivisceral, en bloc, resections are required for patients with T4 tumors. The indications of endoscopic resection techniques are limited to patients with early gastric cancer *i.e.*, Tis or T1a tumors (22).

In the European Society of Medical Oncology (ESMO) guidelines, the role of endoscopic resection as a standalone treatment of gastric cancer is clearly defined. Thus, patient with well differentiated, non-ulcerated, very early gastric cancers (T1a), clearly confined to the mucosa, ≤ 2 cm in diameter are candidates for endoscopic resection. Patients with gastric cancer of more advanced stage *i.e.*, stage Ib–III, should be submitted to distal gastrectomy if a clear macroscopic proximal margin of a least 5 cm can be achieved between the tumor and the gastroesophageal junction. This concept applies for intestinal-type gastric cancers. For gastric cancers of the diffuse type, a clear margin of 8 cm is recommended. If those margins cannot be objectively achieved and guaranteed, a total gastrectomy should be performed (23).

Finally, the Japanese Gastric Cancer Association (JGCA) guidelines take into account the growth pattern of gastric cancer and recommend for T1 tumors a clear margin of >2 cm and for $\geq T2$ tumors, a clear margin of at least 3 cm in case of expansive growth pattern, or a clear margin of at least 5 cm in case of tumors of the infiltrative growth pattern. Whenever these conditions are not fulfilled, the proximal resection margin should be analyzed by frozen sections (24).

Conclusion

In conclusion, the benefits of organ sparing resections become more and more obvious in everyday clinical practice. The preservation of the gastric volume and function appears significantly important in amplifying postoperative nutritional status and in decreasing the incidence of common postgastrectomy complications such as reflux and dumping syndrome. When a tumor in the upper third of the stomach is the case, then things are relatively straightforward and a total gastrectomy is usually the sole valid option. For the rest

tumor sites within the stomach, however, a decision with regards to the oncological appropriateness of a distal gastrectomy should be made. Having in mind, the well documented discrepancy between the gross and pathologic boundaries of the tumor, pitfalls might be encountered. Current published guidelines have used a “safety distance” *i.e.*, >4 or 5 cm between the proximal macroscopic tumor border and the proximal resection margin in order to guarantee a negative resection margin on pathology. An increased distance of safety is currently proposed in high-risk tumors such as tumor of the diffuse histology type.

Conflicts of Interest

The Authors declare no potential conflicts of interest in relation to this study.

Authors' Contributions

Study conception and design: Symeonidis D, Tepetes K; Acquisition of data: Kissa L, Samara A; Analysis and interpretation of data: Petsa E, Samara A; Drafting of manuscript: Symeonidis D; Critical revision: Zacharoulis D, Tepetes K.

References

- Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA and Jemal A: Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 68(6): 394-424, 2018. PMID: 30207593. DOI: 10.3322/caac.21492
- Suh YS, Lee J, Woo H, Shin D, Kong SH, Lee HJ, Shin A and Yang HK: National cancer screening program for gastric cancer in Korea: Nationwide treatment benefit and cost. *Cancer* 126(9): 1929-1939, 2020. PMID: 32031687. DOI: 10.1002/cncr.32753
- Petrillo A and Smyth EC: Multimodality treatment for localized gastric cancer: state of the art and new insights. *Curr Opin Oncol* 32(4): 347-355, 2020. PMID: 32541324. DOI: 10.1097/CCO.0000000000000630
- Song Z, Wu Y, Yang J, Yang D and Fang X: Progress in the treatment of advanced gastric cancer. *Tumour Biol* 39(7): 1010428317714626, 2017. PMID: 28671042. DOI: 10.1177/1010428317714626
- Waddell T, Verheij M, Allum W, Cunningham D, Cervantes A and Arnold D: Gastric cancer: ESMO-ESSO-ESTRO clinical practice guidelines for diagnosis, treatment and follow-up. *Eur J Surg Oncol* 40(5): 584-591, 2014. PMID: 24685156. DOI: 10.1016/j.ejso.2013.09.020
- Jiang L, Yang KH, Chen Y, Guan QL, Zhao P, Tian JH and Wang Q: Systematic review and meta-analysis of the effectiveness and safety of extended lymphadenectomy in patients with resectable gastric cancer. *Br J Surg* 101(6): 595-604, 2014. PMID: 24668465. DOI: 10.1002/bjs.9497
- Symeonidis D, Diamantis A, Bompou E and Tepetes K: Current role of lymphadenectomy in gastric cancer surgery. *J BUON* 24(5): 1761-1767, 2019. PMID: 31786835.
- Brenkman HJF, Tegels JJW, Ruurda JP, Luyer MDP, Kouwenhoven EA, Draaisma WA, van der Peet DL, Wijnhoven BPL, Stoot JHMB, van Hillegersberg R and LOGICA Study Group: Factors influencing health-related quality of life after gastrectomy for cancer. *Gastric Cancer* 21(3): 524-532, 2018. PMID: 29067597. DOI: 10.1007/s10120-017-0771-0
- Takahashi M, Terashima M, Kawahira H, Nagai E, Uenosono Y, Kinami S, Nagata Y, Yoshida M, Aoyagi K, Kodera Y and Nakada K: Quality of life after total vs distal gastrectomy with Roux-en-Y reconstruction: Use of the Postgastrectomy Syndrome Assessment Scale-45. *World J Gastroenterol* 23(11): 2068-2076, 2017. PMID: 28373774. DOI: 10.3748/wjg.v23.i11.2068
- Hosoda K, Yamashita K, Sakuramoto S, Katada N, Moriya H, Mieno H and Watanabe M: Postoperative quality of life after laparoscopy-assisted pylorus-preserving gastrectomy compared With laparoscopy-assisted distal gastrectomy: A cross-sectional postal questionnaire survey. *Am J Surg* 213(4): 763-770, 2017. PMID: 27751530. DOI: 10.1016/j.amjsurg.2016.09.041
- Hu B, El Hajj N, Sittler S, Lammert N, Barnes R and Meloni-Ehrig A: Gastric cancer: Classification, histology and application of molecular pathology. *J Gastrointest Oncol* 3(3): 251-261, 2012. PMID: 22943016. DOI: 10.3978/j.issn.2078-6891.2012.021
- Polkowski W, van Sandick JW, Offerhaus GJ, ten Kate FJ, Mulder J, Obertop H and van Lanschoot JJ: Prognostic value of Laurén classification and c-erbB-2 oncogene overexpression in adenocarcinoma of the esophagus and gastroesophageal junction. *Ann Surg Oncol* 6(3): 290-297, 1999. PMID: 10340889. DOI: 10.1007/s10434-999-0290-2
- Bozzetti F, Marubini E, Bonfanti G, Miceli R, Piano C and Gennari L: Subtotal versus total gastrectomy for gastric cancer: five-year survival rates in a multicenter randomized Italian trial. Italian Gastrointestinal Tumor Study Group. *Ann Surg* 230(2): 170-178, 1999. PMID: 10450730. DOI: 10.1097/00000658-199908000-00006
- Gouzi JL, Huguier M, Fagniez PL, Launois B, Flamant Y, Lacaine F, Paquet JC and Hay JM: Total versus subtotal gastrectomy for adenocarcinoma of the gastric antrum. A French prospective controlled study. *Ann Surg* 209(2): 162-166, 1989. PMID: 2644898. DOI: 10.1097/00000658-198902000-00005
- Bozzetti F, Bonfanti G, Bufalino R, Menotti V, Persano S, Andreola S, Doci R and Gennari L: Adequacy of margins of resection in gastrectomy for cancer. *Ann Surg* 196(6): 685-690, 1982. PMID: 7149820. DOI: 10.1097/00000658-198212001-00012
- Kim BS, Oh ST, Yook JH, Kim HS, Lee IS and Kim BS: Appropriate gastrectomy resection margins for early gastric carcinoma. *J Surg Oncol* 109(3): 198-201, 2014. PMID: 24249119. DOI: 10.1002/jso.23483
- Squires MH 3rd, Kooby DA, Poultsides GA, Pawlik TM, Weber SM, Schmidt CR, Votanopoulos KI, Fields RC, Ejaz A, Acher AW, Worhunsky DJ, Saunders N, Levine EA, Jin LX, Cho CS, Bloomston M, Winslow ER, Russell MC, Cardona K, Staley CA and Maitel SK: Is it time to abandon the 5-cm margin rule during resection of distal gastric adenocarcinoma? A multi-institution study of the U.S. Gastric Cancer Collaborative. *Ann Surg Oncol* 22(4): 1243-1251, 2015. PMID: 25316491. DOI: 10.1245/s10434-014-4138-z
- Berlth F, Kim WH, Choi JH, Park SH, Kong SH, Lee HJ and Yang HK: Prognostic impact of frozen section investigation and extent of proximal safety margin in gastric cancer resection. *Ann*

- Surg 272(5): 871-878, 2020. PMID: 32833759. DOI: 10.1097/SLA.0000000000004266
- 19 Lee CM, Jee YS, Lee JH, Son SY, Ahn SH, Park DJ and Kim HH: Length of negative resection margin does not affect local recurrence and survival in the patients with gastric cancer. *World J Gastroenterol* 20(30): 10518-10524, 2014. PMID: 25132770. DOI: 10.3748/wjg.v20.i30.10518
- 20 Jang YJ, Park MS, Kim JH, Park SS, Park SH, Kim SJ, Kim CS and Mok YJ: Advanced gastric cancer in the middle one-third of the stomach: Should surgeons perform total gastrectomy? *J Surg Oncol* 101(6): 451-456, 2010. PMID: 19924722. DOI: 10.1002/jso.21431
- 21 Hayami M, Hiki N, Nunobe S, Mine S, Ohashi M, Kumagai K, Ida S, Watanabe M, Sano T and Yamaguchi T: Correction to: Clinical outcomes and evaluation of laparoscopic proximal gastrectomy with double-flap technique for early gastric cancer in the upper third of the stomach. *Ann Surg Oncol* 25(Suppl 3): 990, 2018. PMID: 29777403. DOI: 10.1245/s10434-018-6535-1
- 22 National Comprehensive Cancer Network. Gastric Cancer. Version 2019. Available at: <https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1434> [Last accessed on July 27, 2022]
- 23 Smyth EC, Verheij M, Allum W, Cunningham D, Cervantes A, Arnold D and ESMO Guidelines Committee: Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 27(Suppl 5): v38-v49, 2016. PMID: 27664260. DOI: 10.1093/annonc/mdw350
- 24 Japanese Gastric Cancer Association: Japanese gastric cancer treatment guidelines 2014 (ver. 4). *Gastric Cancer* 20(1): 1-19, 2017. PMID: 27342689. DOI: 10.1007/s10120-016-0622-4

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