

Editorial

Quality of Surgery Determinant for the Outcome of Patient With Gastric Cancer

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Curative surgery, the complete removal of the tumor (R0 resection), has long been considered the treatment of choice and the only treatment modality able to provide cure in localized gastric cancer. But until now, the optimal extent of this surgical resection still remains highly debated. Several factors, including tumor stage and difficulties in accurate pre- or intraoperative staging prediction, surgical complications, risks of residual disease and recurrence, as well as quality of life (QOL) differentially influence and complicate the selection of the appropriate extent of surgery.

The term quality of surgery under a wide description should involve both decision making about the optimal extent of surgery and the safe performance of the selected less or more extensive surgery. But until now the interest has almost exclusively been focused on the discussion as whether limited (D1) or extended (D2) node dissection should be performed in all stages, early or late, of cancer and not a tumor stage-oriented approach. Here we discuss the risks and benefits of a tumor stage-tailored surgical strategy that is increasingly receiving attention.¹

Approximately 40%² to 70% of the patients in the Western world¹ and up to 85% in Japan³ have a potentially completely resectable tumor at diagnosis. Formation of secondary tumor(s), recurrence, in these patients after surgical removal of the primary tumor is the cause of treatment failure and death. Recurrence occurs in the gastric bed and perigastric lymph nodes (locoregional), in the peritoneal surface (peritoneal carcinomatosis), and

at distant sites via circulating cancer cells in blood vessels (haematogenous spread) and lymphatic vessels (lymphogenous spread).

The principal goal of surgery, therefore, is to reduce the risk of recurrence. How and why may extent surgery influence recurrence risk and clinical outcomes? Appropriate surgery with sufficient resection margins from the primary tumor and complete dissection of positive nodes can primarily reduce the risk of local and nodal failure, as well as distant recurrence via lymphatic spread. Less favorable seems to be the role of surgery in reducing peritoneal and hematogenous dissemination through less extensive surgical maneuvers.

Locoregional recurrence rates of 40%² after limited “curative” D1 surgery and 20% or less after extended (D2) lymph node dissection^{4,5} reveal the importance of radical surgery in reducing recurrence risk. Although randomized trials^{6,7} with limitations in design and conduction⁸ failed to confirm these difference in recurrence and survival between D1 and D2 groups, current relevant research⁹ confirms the importance of aggressive resection of tumor margins to combat lymphatic dissemination.

Lymphogenic metastasis is an important predictor of survival in gastric cancer. Recent experimental and clinical evidence supports that both vascular endothelial growth factor VEGF-C and VEGF-D induce lymphangiogenesis in tumor^{9–11} and are associated with lymph node metastasis in a variety of human tumors, including gastric cancer.^{12,13} These VEGF-C overexpressing tumors all had functional lymphatic vessels in the tumor margin of a current study.⁹ The researchers conclude that functional lymphatics in the tumor margin are responsible for lymphatic metastasis and, therefore, tumor margins should be treated aggressively by surgery.⁹ However, at clinical detection of most tumors, cancer cells have already spread via the lymphatic system to the nearby lymph nodes or distant organs.

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Approximately 30% of the patients with a curable tumor⁸ have positive level 2 nodes (N2 disease in the Japanese anatomical classification¹⁴), and thus an R0 resection can be achieved only by a D2 and not a D1 node dissection.⁸ But D2 dissection is associated with longer time consumed and increased morbidity and mortality risk than D1 dissection^{6,7} by lack of surgical experience.⁸ For this reason, as well as whether the advantage of D2 dissection in the reduction of residual nodal disease and recurrence rate may also be translated into an evidence-based survival benefit, the extent of lymph node dissection is highly debated.⁶⁻⁸ Surgical decision on extent of node dissection should consider several parameters and balance risks and benefits.

Today, the most realistic way to combat metastatic nodal disease and to prevent further lymphatic spread at distant organs is provided by appropriate surgical lymphadenectomy. The future of prevention and treatment of lymphatic metastasis may involve a combination of both optimal surgery⁸ and antilymphangiogenic therapy with the use of agents such anti-VEGF-C, anti-VEGF-D, and other molecules that block different steps in lymphatic metastasis.^{10,15,16}

The extent of stomach resection, distal subtotal, proximal, or total gastrectomy, has long been established. Tumor site and histology according to Lauren classification, more extensive surgical margins for diffuse type rather than intestinal type of cancer, are the criteria for decision making.¹ However, there is now a trend toward less extensive gastric resection in early-stage tumors for the improvement of QOL. The effectiveness of endoscopic mucosal resection (EMR), pylorus-preserving surgery, and laparoscopic wedge resection is now being investigated. EMR provides excellent QOL and probably does not increase risks of recurrence and death¹⁷ when the selection criteria of size (<2 cm), depth of invasion (mucosal cancer), and histology (intestinal type) are met.¹⁸ EMR is advocated as the primary treatment of choice in Japan¹⁸ although there is still no confirmation from randomized trial. The very small proportion of early-detected mucosal cancers is the major limitation of such strategy in the Western world.

Another important matter of discussion in the surgical treatment of gastric cancer is whether and when gastrectomy combined with an additional organ resection might be beneficial. Over the past two decades splenectomy or pancreaticosplenectomy was often performed in all stages of cancer and was involved in the design of two recent randomized trials.^{6,7} However, this aggressive surgery increases operative morbidity and mortality without survival improvement.^{1,6-8} Interestingly, this additional organ resection was pathologically confirmed as T4 dis-

ease in only 14%¹⁹ suggesting that in most cases additional organ resection is in fact unnecessary for an R0 resection. Accumulating evidence supports that prophylactic resection of the spleen, pancreas, or other organ does more harm than benefit and should not be performed. The resection of the spleen particularly suggests caution because of the possible immunologic role of the spleen against postoperative infections and tumor recurrence.¹

However, in advanced T4 cancers extensive radical surgery, including additional organ resection is needed to accomplish an R0 resection. This aggressive surgical approach can be performed safely and can improve overall survival according to a current report from a specialized institution,¹⁹ but it usually increases the risk of operative morbidity and mortality. Whether this primary surgery or neoadjuvant treatment for tumor reduction and subsequent surgical resection for localized advanced disease is more beneficial remains unclear and is being investigated in randomized trials.

Accumulating evidence indicates that extent of surgical procedure strongly influences recurrence rate and survival on one side and complications and QOL on the other. The more extensive the surgery the lower the risk of residual disease, recurrence, and death, but the higher the rates of operative morbidity the more adverse effects on QOL. Thus, decision regarding extent of surgery is a balance of risks and benefits. Because less extensive surgery is not associated with increased risk of recurrence in earlier-stages cancer, preoperative accurate prediction of tumor spread (staging) is a determinant for decision making. However, despite advances in imaging technology, endoscopic ultrasonography, computer tomography, magnetic resonance imaging, and positron emission tomography, which have increased substantially the accuracy of tumor depth (T stage) and distant metastasis (M stage), prediction rate of nodal status is not high as to allow with safety decision about lymphadenectomy.

Ideally, if the tumor stage could be accurately predicted, optimal surgery might be focused on the minimum extent of surgery needed to accomplish an R0 resection with sufficient resection of tumor margins. This tumor stage-oriented procedure then involves a wide spectrum of treatments from minimally invasive approaches (EMR, laparoscopic approach, function-preserving gastrectomy) to aggressively extensive resections; however, such strategy requires numerous conditions including the availability of expertise teams of surgeons, oncologists, and endoscopists, as well as modern diagnostic and therapeutic technology. In many regional hospitals in the Western world a change from

standard D1 resection to less or more extensive resections is and will remain challenging.

A new era toward a tumor stage based on less or more extensive surgery in the management of gastric cancer has already been started. However, caution suggests that the effectiveness of this strategy in improving survival and QOL, as compared with the standard surgical procedure, has not yet been proven in randomized trial. At present, this surgical approach is used in a few specialized institutions, particularly in Japan, but with increased experience and improvements in accurate tumor staging prediction therapeutic technology is expected to be used wider in the future. Given that, any adjuvant treatment is of little effectiveness in improving survival.²⁰ The quality of surgery in both decision making and performance of optimal extent of surgery with minimal morbidity is determinant for both survival and QOL.

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