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**SECRETS OF THE THERAPEUTIC STRATEGY FOR OESOPHAGEAL AND GASTRIC CANCER**

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QUARTERLY PUBLICATION OF THE HELLENIC SOCIETY OF SURGICAL ONCOLOGY

# CONTENTS

*Dear Colleagues,*

*The present and the previous issue of the official journal of the Hellenic Society of Surgical Oncology, Hellenic Surgical Oncology, are dedicated to the first special congress entitled "Secrets of the therapeutic strategy for oesophageal and gastric cancer", which will take place the 26th and 27th of February 2016 in Thessaloniki, Greece. It is beyond any doubt that the Organizing Committee of the Congress under the Presidency of Professor Ioannis Kanellos and Assistant Professor Konstantinos Sapalidis is the guarantee of a successful meeting.*

*This issue of Hellenic Surgical Oncology contains manuscripts submitted by speakers who responded to the call for papers. In each manuscript the distinguished speakers discuss the topic of their presentation at the congress. While the previous issue contained the manuscripts pertaining to oesophageal cancer, those regarding gastric cancer have been collected in the present issue of the Journal.*

*Moreover, it is my pleasure to announce that the manuscripts of the present issue, as well as the past and coming issues of the Journal will be soon accessible on the Journal's own website in order to further facilitate its accessibility.*

*It is probably unnecessary to mention that it will be our great pleasure to receive interesting papers from you for publication in the official journal of the Society. Our aim is a high quality Journal which features superior clinical studies (from Greece and abroad), substantial observational data and interesting cases, discusses points of view and updates our readers on recent advances by publishing outstanding reviews and relevant breaking news in the various fields of Surgical Oncology.*

Sincerely yours,

**Eelco de Bree**
Editor-in-Chief

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REVIEW

# Etiology of gastric cancer
## Hereditary diffuse gastric cancer

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**ABSTRACT**

**Gastric cancer ranks as the forth most common cancer worldwide. Its etiology remained elusive and seemed multifactorial till recent times, with more attention being focused on lifestyle, dietary and racial factors. In nowadays interest started to shift to other possible causes and may be more significant, such as bacterial infection with helicobacter pylori (H. pylori). The bacterial infection is thought to play a key role in the development and progress of gastric cancer. In addition another issue concerning the gastrointestinal surgeon is the awareness of the presence of hereditary diffuse gastric cancer. This awareness, will allow for the necessary steps to be taken in prevention as well as treatment of this form of gastric cancer.**

**KEY WORDS:** gastric cancer, H. pylori, bacterial infection

Gastric cancer is the fourth most common cancer worldwide. Throughout the 20thcentury the etiology of gastric cancer was mainly focused on racial, lifestyle, and dietary criteria. Thus it is much more common in Asian populations. The risk of gastric cancer for example in Japan is as much as eight times higher in comparison with the United States. This realization has been associated most probably with dietaryhabits (salted food being more popular in Asia than in western societies). In addition the consumption of preserved or processed food increases the risk of development of gastric cancer. This comes as a result of elevated levels of nitrate products. Several ongoing EPIC (European Prospective Investigation into Cancer) studies confirm the association of consumption of preserved foods with increased incidence of gastric cancer. As well as other EPIC studies have shown the protective benefits of Vit C, through prevention of damage of the cells lining the stomach wall. Fruits and vegetables also seem to have a protective effect due to their antioxidant abilities. Smoking and alcohol consumption seem also to be risk factors in developing gastric cancer. Also pernicious anemia and blood group A. Peptic ulcer disease has also been implicated as a risk factor. Much attention in recent years though, apart from the classical nutritional studies, has been payed in the role of H. pylori infection and gastric cancer. It has been investigatedextensively in recent years. H. pylori infection increases the

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risk of developmentgastric cancer bysix times. Of course it is obvious that not all of the patients that suffer from H. pylori infection will develop gastric cancer. It seems likethat the chronic atrophic gastritis caused by the persistinginflammation in conjunction with other mentioned risk factors, such as smoking alcoholconsumption and dietary habits play an accumulative role in the development of gastric cancer. A positive family history is also a risk factor in families with non-hereditary gastric cancer. Special care should be taken for patients with inheritedsyndromes. These patients account for up to 3% of all diagnosed cases and genetic counseling is required. Hereditary diffuse gastric cancer is inherited by an autosomal dominant pattern and is caused by a mutation of CDH 1 gene. Families that meet certain criteria should be genetically tested in order to discover if this mutation exists. These criteria include an individual within the family with diffuse gastric cancer under the age of forty, or families with two cases of gastric cancer with one at least being of the diffuse type. Presence of positive CDH 1 gene caries a lifetime risk of up to 80% in developing gastric cancer for both men and women. In addition an up to 50% lifetime time risk of development of lobular cancer in women. Prophylactic gastrectomy should be considered in asymptomatic carries of the gene, even if endoscopy appears normal. In women especially, regular screening with breast imaging including mammograms and ultrasounds were required.

In conclusion, the etiology of gastric cancer seems to be more complicated then recently thought. Much more attention was given in the past to dietary habits and how these were influencing the development of gastric cancer. Many investigations were dedicated in proving the protective or destructive properties of different types of foods on the lining of the stomach. In recent years the increased importance of H. pylori has been highlighted in the pathogenesis of gastric cancer. Of course no one factor can be explicitlyblamed for the development of gastric cancer. All play their distinct part in the multifactorial etiology. In addition the modern G.I. surgeon must be aware of the entity of hereditary diffuse gastric cancer. It might represent only a small portion of the total number of patients, but if detected can completely change the course of treatment as well screening of entire families.

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REVIEW

# Gastric cancer – Staging systems

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**ABSTRACT**

**Gastric cancer is a common tumor and for its description two staging systems have been introduced, the Union for International Cancer Control (UICC/TNM) classification and the Japanese Classification of Gastric Carcinoma (JCGC). The two systems go through continuous corrections and show differences between each edition. However, the efficiency of each one is still controversial and many studies comparing these forms of classifications have been realized. More studies are needed for safer results considering future prognosis.**

**KEY WORDS:** gastric cancer, staging, TNM system

## INTRODUCTION

Gastric cancer is a high morbidity and mortality malignant tumor, with a survival rate less than 30% and 800,000 deaths annually.[1] The highest rates of its presence are located in Japan, China, Eastern Europe, and South America.[2] The characteristics of the disease have shown the necessity of an accurate staging system that could provide a common language for further research, prognosis and treatment.

## UICC/TNM AND JCGC GRADING SYSTEM

The Union for International Cancer Control (UICC) has introduced the TNM classification that has been used during the last 50 years as a standard of cancer staging. T describes the primary tumor site, N describes the regional lymph node involvement and, finally, M describes the presence of distant metastatic spread. A revised 7th edition for the TNM staging of gastric cancer has been published in 2010 (Tables 1-4) in order to clarify the characteristics of tumors arising in the gastric cardia or the esophagogastric junction.[2] A tumour the epicentre of which is within 5 cm of the oesophagogastric junction and also extends into the oesophagus is classified and staged according to the oesophageal scheme.

On the other hand, Japanese research for gastric cancer has been revealing and a Japanese classification of gastric carcinoma (JCGC) has also been proposed.[3] The disadvantages of this staging include ambiguity in lymph node grading and

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**Table 1.** T definitions

| | |
|---|---|
| TX | Primary tumor cannot be assessed |
| T0 | No evidence of primary tumor |
| Tis | Carcinoma in situ; intraepithelial tumor without invasion of the lamina propria |
| T1 | Tumor invades lamina propria; muscularis mucosae, or submucosa |
| T1a | Tumor invades lamina propria or muscularis mucosae |
| T1b | Tumor invades submucosa |
| T2 | Tumor invades muscularis propria |
| T3 | Tumor penetrates subserosal connective tissue without invasion of visceral peritoneum or adjacent structures. T3 tumors also include those extending into the gastrocolic or gastrohepatic ligaments, or into the greater or lesser omentum, without perforation of the visceral peritoneum covering these structures |
| T4 | Tumor invades serosa (visceral peritoneum) or adjacent structures |
| T4a | Tumor invades serosa (visceral peritoneum) |
| T4b | Tumor invades adjacent structures such as spleen, transverse colon, liver, diaphragm, pancreas, abdominal wall, adrenal gland, kidney, small intestine, and retroperitoneum |

**Table 2.** N definitions

| | |
|---|---|
| NX | Regional lymph node(s) cannot be assessed |
| N0 | No regional lymph node metastasis |
| N1 | Metastasis in 1 to 2 regional lymph nodes |
| N2 | Metastasis in 3 to 6 regional lymph nodes |
| N3 | Metastasis in 7 or more regional lymph nodes |

**Table 3.** M definitions

| | |
|---|---|
| M0 | No signs of metastases |
| M1 | Metastatic disease |

**Table 4.** TNM stages

| | |
|---|---|
| 1a | T1N0M0 |
| 1b | T2N0M0, T1N1M0 |
| 2a | T3N0M0, T2N1M0, T1N2M0 |
| 2b | T4aN1M0, T3N1M0, T2N2M0, T1N3M0 |
| 3a | T4bN0M0, T3N2M0, T2N3M0 |
| 3b | T4bN0M0, T4bN1M0, T4aN2N0, T3N3M0 |
| 3c | T4bN2M0, T4bN3M0, T4aN3M0 |
| 4 | any T any N M1 |

grading according to the location and the section to be dissected.[4]

## COMPARISON BETWEEN 6TH AND 7TH UICC SYSTEM

The comparison between the two different staging systems, as well as between their previous forms, has been necessary for their further evaluation. Therefore, comparing the 6th and 7th UICC TNM edition, both editions of the AJCC staging system have a limitation for T1 gastric cancer (early gastric cancer).[5] The 7th TNM edition does not always seem to be superior to the 6th edition in the case of prognosis after curative resection for advanced gastric cancer. Extended node dissection may be effective for N0-N3a, but not for N3b and M1 stages,[6] but the increased complexity of the 7th edition should also be balanced with improved prognostic accuracy.[7]

## COMPARISON BETWEEN THE UICC AND THE JCGC SYSTEM

Both the 13th JCGC and 7th UICC systems are able to accurately estimate the prognosis, but the use of the UICC system may be simpler and easier.[8] However, according to a study of Yamashita et al,[9] the JCGC system is superior to the UICC system about the prognosis of stage IIIA, IIIB, and

IV cancers, but invasion or not of the muscularis propria is also important. Moreover, the presence of undifferentiated components in differentiated T1/T2 gastric cancer, that is associated with tumor progression, is better described in UICC than the JCGC system.[10] Finally, correlation of histology and nodal staging is better in the 13th JCGC system than the 6th UICC and 14th JCGC/7th systems.[11] Considering these interesting, yet equivocal results, further investigation of the correctness of each system is needed.

## FUTURE PERSPECTIVES

AJCC does not determine the radiological signs that describe every single stage, so standardization of the examination and the overall process (oral filling, multi-phase enhancement, multi planar reconstruction, window width, etc.), the exploration of the fine signs and new modalities (spectral CT, diffusion weighted MRI) could be useful.[12] The number and location of metastatic lymph nodes for the prognosis after radical surgery,[13] as well as consideration of extracapsular lymph node involvement, that is associated with higher stages and is considered as an independent negative prognostic factor should also be involved in future staging systems.[14]

## CONFLICT OF INTEREST

The author declares that he has no conflict of interest.

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REVIEW

# The role of endoscopic ultrasonography in gastric cancer

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## INTRODUCTION

Gastric cancer is one of the commonest malignancies worldwide, and both the prognosis and survival rate are poor for advanced stages.[1] Currently, the surgical approach is the only curative treatment, but few patients are candidates for resection at the time of presentation.[2] Therefore, an accurate preoperative staging allows rational treatment selection. Strategies range from endoscopic mucosal resection to preoperative neoadjuvant therapy, which is strongly recommended for locally advanced cases (with serosal invasion and/or nodal involvement).[3,4] Endoscopic ultrasonography (EUS) and multidetector computed tomography (MDCT) are the commonest techniques in the staging of gastric cancer, despite conflicting results having been reported.[5-7]

EUS is invasive but capable of detecting all the wall layers and is regarded as the modality of choice for local staging, with an accuracy ranging from 65 to 92.1% for T stage [8] and from 66 to 90% for N stage.[9,10] However, this technique has a restricted field of view for nodal involvement, is highly operator dependent and cannot detect distant metastases.

Conversely, MDCT is non-invasive and is able to assess the presence of distant metastases. Its accuracy has constantly improved, for detecting both the invasion of gastric wall, ranging from 69 to 89%,[11-13] and nodal

involvement, ranging from 69 to 92%.[14,15] Nevertheless, MDCT involves the use of ionizing radiation and cannot adequately differentiate all the gastric wall layers.

Recent advances in magnetic resonance imaging (MRI) [e.g. breath-hold sequences and diffusion-weighted imaging (DWI)] have improved the value of MRI for abdominal imaging, including imaging of gastric cancer;[16] in particular, on DWI pathological tissue is characterized by higher signal intensity than normal structures[17]. MRI studies report an accuracy ranging from 73.5 to 87.5% for T stage [18,19] and from 55.2 to 65% for N stage.[19,20] As is widely recognized, this technique provides high soft tissue contrast but has long acquisition times; moreover, motion artefacts (peristalsis, cardiovascular pulsation) are some important limitations.

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## USE OF EUS IN THE TREATMENT OF GASTRIC CANCER

In the treatment of early gastric cancer, ESD is the safest and most effective treatment. As experience in ESD increases and various accessories develop, it is increasingly possible to remove lesions irrespective of the area and size. Lesions that can be removed remove via ESD are those that have not deeply invaded the submucosa and do not have lymph node metastasis. Many imaging methods have been used, but there are no diagnostic methods for predicting lymph node metastasis accurately in stomach cancer.

EUS is useful in choosing a treatment approach for lesions in which invasion to the submucosa is suspected upon examination of the gross endoscopic appearance or for gastric adenomas or mucosal cancers detected by pathologic examination. Moreover, in cancers of a size where ESD is likely to be an extensive process, EUS may be used before ESD. In the case of large lesions, EUS may find sites of blood vessels within a tumor before ESD, preventing excessive blood loss. However, when ulcers or fibrotic lesions are present, the depth of invasion is most likely exaggerated and some patients who might otherwise receive endoscopic resection (ER) may be treated by unnecessary surgery. The pattern analysis by Kida is useful for such patients.

## THE ROLE OF EUS IN T STAGING

Classifying lesions with submucosal invasion before surgery ensures an accurate prognosis and is necessary for surgical planning. When restricted to the results of the endoscopy examination alone, the evaluation of invasion depth has many limitations. Puli et al[21] published the results of a meta-analysis including 22 studies to evaluate the usefulness of EUS in stomach cancer, and the sensitivity and specificity by stage were, respectively, 88.1% and 100% for T1, 82.3% and 95.6% for T2, 89.7% and 94.7% for T3, and 99.2% and 96.7% for T4 staging. Incidentally, EUS for T stage detection was more accurate in advanced cancer than in early cancer.[21] Mocellin et al[22] analyzed the distinction between T3-4 and T1-2 lesions, and EUS showed 86% sensitivity and 91% specificity.

To determine suitable patients for ER using EUS, it is necessary to accurately interpret EUS images. Mouri et al[23] evaluated the usefulness of EUS for determining the applicability of ESD and visualizing invasion depth in early gastric cancer. The EUS-mucosa (M) and EUS-M/submucosa (SM) borders had no tumor cells in the vertical margins in all patients who underwent ESD, and were good indicators for ER.[23]

## THE DIAGNOSTIC VALUE OF EUS IN N STAGE

The AJCC 7th edition TNM classification of gastric cancer made an important change to the classification of lymph node metastasis lesions. The previous edition classified 1 to 6 lymph node lesions as N1, whereas the present edition defines N1 as having 1 to 2 lymph node lesions and N2 as 3 to 6 metastasized lymph nodes. The accuracy of EUS pre-surgical N stage evaluation is approximately 65% to 95%.[24] Cardoso et al[25] conducted a meta-analysis regarding pre-surgical N stage evaluation (N0 vs. N+), and they reported an accuracy of 64%, sensitivity of 74%, and specificity of 80%. The accuracy was unsatisfactory because of the difficulty in identifying changes in the lymph nodes due to inflammation and metastasized lymph nodes, and because there is a low possibility of detecting metastasized lymph nodes that are distant from the lesion.

## EUS VS. CT IN PREOPERATIVE EVALUATION

The mainstay examination before gastric cancer surgery is CT. Studies regarding early cancer for penetration depth using CT have reported unsatisfactory results, but the development of

multidetector computed tomography (MDCT) has increased the accuracy of T stage evaluation. EUS is the preferred modality for determining invasion depth, but is limited in evaluating distant metastasis. The accuracy of T stage determination with EUS and CT was 65% to 92% and 77.1% to 88.8%, respectively.[26] For N stage evaluation, the sensitivity and specificity were, respectively, 71% and 49% for EUS, and 80% and 78% for MDCT.[27]

Peritoneal invasion must be detected on pre-surgical examination to avoid unnecessary surgery. In diagnosing T4 tumors (serosa), the sensitivity and specificity of EUS were 77.8% to 100% and 67.9% to 100%, respectively, and that of CT was 82.8% to 100% and 80% to 96.8%, respectively.[26] For detecting peritoneal metastases, the sensitivity and specificity were, respectively, 34% and 96% for EUS, 33% and 99% for CT, and 28% and 97% for PET.[28]

## RESULTS OF A META-ANALYSIS

Recently, a meta-analysis[29] concerning diagnostic accuracy of EUS for the preoperative locoregional staging of primary gastric cancer has been published. For primary tumor (T) stage, results were stratified according to the depth of invasion of the gastric wall. The meta-analysis of 50 studies (n = 4397) showed that the summary sensitivity and specificity of EUS in discriminating T1 to T2 (superficial) versus T3 to T4 (advanced) gastric carcinomas were 0.86 (95% confidence interval (CI) 0.81 to 0.90) and 0.90 (95% CI 0.87 to 0.93) respectively. For the diagnostic capacity of EUS to distinguish T1 (early gastric cancer, EGC) versus T2 (muscle-infiltrating) tumors, the meta-analysis of 46 studies (n=2742) showed that the summary sensitivity and specificity were 0.85 (95% CI 0.78 to 0.91) and 0.90 (95% CI 0.85 to 0.93) respectively. When we addressed the capacity of EUS to distinguish between T1a (mucosal) versus T1b (submucosal) cancers the meta-analysis of 20 studies (n=3321) showed that the summary sensitivity and specificity were 0.87 (95% CI 0.81 to 0.92) and 0.75 (95% CI 0.62 to 0.84) respectively. Finally, for the metastatic involvement of lymph nodes (N-stage), the meta-analysis of 44 studies (n = 3573) showed that the summary sensitivity and specificity were 0.83 (95% CI 0.79 to 0.87) and 0.67 (95% CI 0.61 to 0.72), respectively.

## AUTHORS' CONCLUSIONS OF THE META-ANALYSIS

By analyzing the data from the largest series ever considered, we found that the diagnostic accuracy of EUS might be considered clinically useful to guide physicians in the locoregional staging of people with gastric carcinoma. However, the heterogeneity of the results warrants special caution, as well as further investigation for the identification of factors influencing the outcome of this diagnostic tool. Moreover, physicians should be warned that EUS performance is lower in diagnosing superficial tumors (T1a versus T1b) and lymph node status (positive versus negative). Overall, we observed large heterogeneity and its source needs to be understood before any definitive conclusion can be drawn about the use of EUS can be proposed in routine clinical settings.

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REVIEW

# The role of intraperitoneal chemotherapy in gastric cancer

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## ABSTRACT

**Peritoneal carcinomatosis of gastric cancer represents advanced malignant disease and is associated with a grim prognosis. Systemic chemotherapy is not very effective in these cases. Although peritoneal carcinomatosis is categorised as metastatic disease, it represents a special disease pattern considered to be a locoregional disease limited to the abdominal cavity, suggesting a potential efficacy of locoregional treatment such as intraperitoneal chemotherapy. Intraperitoneal chemotherapy, either as postoperative or as hyperthermic intraoperative intraperitoneal chemotherapy, has been used as adjuvant treatment to reduce the risk of peritoneal carcinomatosis in high-risk gastric cancer and in combination with cytoreductive surgery as locoregional treatment for selected gastric cancer patients with peritoneal carcinomatosis. Moreover, it has been used as neoadjuvant treatment and as treatment of refractory ascites in patients with peritoneal carcinomatosis of gastric origin. The pathophysiology of peritoneal carcinomatosis as well as the rationale and principles of cytoreductive surgery and intraperitoneal chemotherapy are stressed. The current data of clinical studies on intraperitoneal chemotherapy in gastric cancer are reported and discussed. The role of intraperitoneal chemotherapy in the treatment of peritoneal carcinomatosis of gastric origin is still evolving and needs larger studies before it can be accepted as a standard of care.**

**KEY WORDS:** gastric cancer, intraperitoneal chemotherapy, peritoneal carcinomatosis

## INTRODUCTION

Peritoneal carcinomatosis (PC) represents advanced malignant disease and has generally been associated with a grim prognosis. PC occurs synchronous with the primary tumour in about 14-43% of patients with gastric cancer and accounts for 35% of all synchronous metastases.[1] It may be the sole site of synchronous metastasis in 9% of patients with gastric cancer.[1] Peritoneal recurrence is seen in 10-46% of patients after curative surgery for gastric cancer and it accounts for 36-45% of all recurrences.[1,2] The peritoneum is the first/sole site of tumour recurrence after D2 gastrectomy in 12-40% of patients.[2] Patients with gastric PC have a poor response to systemic chemotherapy, resulting in median survival of approximately 10-18 months.[3-5]

Peritoneal surface malignancy is often the

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major source of morbidity and mortality and of major concern in cancer management. Although PC is categorised to be metastatic disease, it represents a special disease pattern considered a locoregional disease limited to the abdominal cavity. Intraperitoneal chemotherapy has been used as locoregional treatment to prevent, or to treat, patients with PC from gastric, colorectal and ovarian cancer, with mesothelioma and with pseudomyxoma peritonei.[6,7]

The aim of this review is to present the current data on the role of intraperitoneal chemotherapy in gastric cancer. However, firstly, the pathophysiology of PC as well as the rationale and principles of cytoreductive surgery (CRS) and intraperitoneal chemotherapy will be briefly discussed.

## PATHOPHYSIOLOGY OF PERITONEAL CARCINOMATOSIS IN GASTRIC CANCER

In order to appreciate the role of intraperitoneal chemotherapy, it is important to understand the pathogenesis of PC of gastric origin. Intra-abdominal recurrence after curative resection usually originates from intraperitoneal free cancer cells, which in turn can occur from two potential sources: spontaneous exfoliation of cancer cells from the primary tumour, and traumatic dissemination of cancer cells as a result of the surgical trauma.[8-10] Intraperitoneal free cancer cells can be seen in up to 24% patients with stage I and 40% patients with stage II or III gastric cancer.[11] The spontaneous seeding of cancer cells is more frequent in gastric cancer involving the serosal surface of the stomach since this predisposes to exfoliation of the cancer cells. During radical surgery for gastric cancer, cancer cells are released from transected lymphatic channels, tissue at the narrow margins of resection, and tumour-contaminated blood lost in the surgical field from the cancer specimen.[8,12,13] Yu et al[14] observed that in a cohort of patients undergoing a D2 gastrectomy, only 24% had a positive cytology on peritoneal lavage just before the gastrectomy, whereas nearly 58% had a positive cytology in the lavage done immediately after the surgery, suggesting that surgery is responsible for dissemination of tumour cells into the peritoneal cavity. Once the cancer cells gain access to the peritoneal cavity, they spread to various areas aided by gravity, intestinal peristalsis and negative pressure due to movement of the diaphragm. Adjuvant intraperitoneal chemotherapy is therefore intended to clear these intraperitoneal free cancer cells which persist after a curative resection. The above described pathophysiology demonstrates why adjuvant intraperitoneal chemotherapy may be considered in gastric cancer for serosal invasion and nodal disease.

## RATIONALE FOR INTRAPERITONEAL CHEMOTHERAPY AND PREREQUISITES

Conventional treatment of PC includes (palliative) surgery and systemic chemotherapy. However, surgery leaves behind at least some microscopic disease and systemic chemotherapy is generally ineffective due to poor drug penetration.[6] Although usually considered to be systemic disease, PC can be better understood as regional dissemination. Many intra-abdominal malignancies with tumour implants on peritoneal surfaces may remain confined to the peritoneal cavity for a prolonged period of time. This means that even though it is certainly considered a poor prognostic sign, it is not proof of distant metastases, thus providing a rationale for regional cancer treatment.[7]

The main advantage of intraperitoneal chemotherapy is its ability to achieve a significantly higher concentration of chemotherapy in the locoregional area, resulting in improved efficacy.[5] The administration of chemotherapy into the peritoneal cavity does not only ensure better tumour tissue exposure to the drug, but also minimises the systemic toxicity as only a limited portion of the drug is absorbed from the peritoneal cavity into the systemic vascular circulation.[15] Further, the vascular

drainage from a large portion of the peritoneum is through the portal venous system, allowing for early metabolism and inactivation of the drug in the liver.[15] Intraperitoneal chemotherapy can be delivered intraoperatively in combination with mild hyperthermia (40-43ºC), which itself is in some degree toxic to the cancer cells and, probably more importantly, enhances the efficacy of many chemotherapeutic drugs.

Intraperitoneal chemotherapy needs to fulfil some prerequisites in order to be effective.[15] In the case of PC, extensive CRS leaving no, or very small macroscopic disease behind, should always precede intraperitoneal chemotherapy, since the penetration of the intraperitoneally delivered drug into tumour deposits is limited. CRS should not be confused with debulking surgery, which is surgery aimed to reduce gross tumour burden. The ultimate goal of CRS is to remove all macroscopic peritoneal disease. Optimal or complete CRS may be achieved by performing the peritonectomy procedures which have been well-described by Sugarbaker.[16] Additionally, resection of other involved organs are usually necessary. These extended and multi-visceral resections should be performed only if an optimal or complete CRS can be achieved.[17]

Intraperitoneal chemotherapy is generally used intra- or postoperatively because in the case of PC CRS is required and in an adjuvant setting a gastrectomy has to be performed first. Intraoperative and early postoperative intraperitoneal therapy are intended to consolidate the effect of surgery by destroying residual small tumour noduli and microscopic intraperitoneal malignant cell nests. In postoperative intraperitoneal chemotherapy, drugs have to be administered during the first postoperative days, before any new surgery-related adhesions are produced. When adhesions form in some areas of the peritoneal cavity, the tumouur cells may not be reached with the intraperitoneal chemotherapy.[18] Late postoperative intraperitoneal chemotherapy, i.e. longer a than 2 week time lapse after surgery, is associated with diminished therapeutic effect, probably due to uneven peritoneal distribution caused by postoperative adhesions, and peritoneal cavity access catheter related problems.[19]

Because the administered drug solution has to reach the entire seroperitoneal surface, an adequate volume of the carrier solution during the entire treatment is required. The choice of the chemotherapeutic drug that is to be used during intraperitoneal chemotherapy is very important and certain aspects have to be taken into account. These are described in detail elsewhere.[20,21] In short, the agent should lack local toxicity and need of metabolisation in its active form (usually in the liver), be direct cytotoxic, have a well established activity against the malignancy being treated and demonstrate a pharmacokinetic advantage after intraperitoneal administration with high locoregional drug exposure and limited systemic toxicity. When the drug is used during hyperthermic intraperitoneal chemotherapy (HIPEC), a synergistic effect with heat is preferred, as increased temperature may enhance the responsiveness of the tumour cells to the cytotoxic agents.[22] Hence, the drug of choice for intravenous administration is not necessarily the one that is optimal for intraperitoneal chemotherapy. More favourable pharmacokinetics and thermic enhancement may make a systemically less effective drug highly advantageous for intraperitoneal chemotherapy. In gastric cancer, mitomycin C and cisplatin are often used for HIPEC because of their synergistic effect with hyperthermia. Docetaxel, paclitaxel and 5-fluorouracil are attractive drugs for intraperitoneal chemotherapy because of their favourable pharmacokinetic profile, resulting in high and prolonged intraperitoneal drug concentrations.[20,21]

It is of utmost importance to carefully select patients who may benefit from this major procedure and to avoid its morbidity and mortality in patients who are not expected to benefit. When evaluating a patient for CRS and intraperitoneal chemotherapy, the surgeon should take into account the tumour biology and the extent of the

disease as well as the patient's age and comorbidities which may compromise the intra- and postoperative course.[23] The patient should be adequately fit to undergo this major multimodality treatment. Most importantly, preoperative evaluation should assess whether optimal or complete CRS is feasible in the individual patient. Widespread and high volume peritoneal disease, extensive involvement of small bowel or mesenterium, more than one bowel stenosis, large tumour masses in the lesser omentum, extensive disease in the hepatoduodenal ligament, biliary or uretral obstruction due to penetration through the peritoneum (and not due to external compression) and para-aortic lymph node metastases are usually considered to be contraindications because they are suggestive of aggressive biological behaviour, decreased probability of optimal or complete CRS and poor outcome. This approach usually seems to be contraindicated when extra-abdominal metastases and liver metastases are present, since the biology of these tumour locations will not be influenced by the locoregional treatment. Radiological investigations such as computed tomography (CT) magnetic resonance imaging (MRI) and position emission tomography (PET) have been used to assess the above mentioned criteria which aim for improved preoperative patient selection.[24] Although in the past CT was not very accurate in depicting peritoneal tumour deposits,[25] modern contrast-enhanced multi-sliced CT is regarded as the fundamental imaging modality, whilst MRI, PET, laparoscopy and serum tumour markers are judged worthy of being taken into consideration, but not-essential.[26] CT-enteroclysis gives information about small bowel and mesenterium involvement.[27]

The case of each patient who is a potential candidate for CRS and perioperative intraperitoneal chemotherapy should be discussed in a multi-disciplinary team.[23] When considered a good candidate, different parts of the treatment have to be discussed with the patient in detail, referring in particular to the probabilities of various organ resections, ostomies, postoperative morbidity, quality of life and risk of recurrence. Moreover, the individual patient's motivation is of importance as it will influence the whole postoperative course.[23]

## CLINICAL STUDIES OF INTRAPERITONEAL CHEMOTHERAPY IN GASTRIC CANCER

As discussed above, peritoneal metastases are present in a significant proportion of patients undergoing potentially curative surgery for gastric cancer or are detected during follow-up as recurrent disease. The efficacy of systemic chemotherapy is very limited, resulting in a median survival of 10-18 months.[3-5] Intraperitoneal chemotherapy has been mainly used in an attempt to reduce the risk of PC in high-risk gastric cancer, usually defined as tumours with serosal invasion or nodal disease, or after CRS for evident PC.

### Adjuvant treatment

In a meta-analysis of 13 randomised trials on any type of adjuvant intraperitoneal chemotherapy for resectable high-risk gastric cancer which were published up to 2005,[28] overall survival was improved by this treatment modality. With the adjuvant administration of HIPEC a 40% reduction in mortality was achieved (p=0.002), while for the combination of HIPEC and early postoperative intraperitoneal chemotherapy a 55% reduction in mortality was found (p=0.0002). Normothermic intraoperative intraperitoneal chemotherapy was associated with a trend towards improved survival (hazard ratio (HR) 0.67, p=0.06). Both early and delayed postoperative chemotherapy did not significantly alter overall survival (HR 0.67, p=0.11 and HR 0.89, p=0.68, respectively). In some of the included studies, locoregional recurrence had been noted. Surprisingly, the risk of locoregional recurrence was not significantly reduced after hyperthermic or normothermic intraoperative intraperitoneal chemotherapy after meta-analysis. Only in one single study on early postoperative

intraperitoneal chemotherapy,[29] was the locoregional recurrence rate significantly reduced (HR 0.51, p=0.008). Although HIPEC was found to be associated with improved survival, the question of its efficacy in preventing locoregional recurrence could not be answered directly from the present study.[28] It is acknowledged that this may be partly attributed to inadequacy of intensive follow-up and difficulty in accurately detecting peritoneal recurrence with radiologic modalities. The perioperative mortality, the anastomotic leakage rate and the incidence of bowel and pancreatic fistula were not increased by adjuvant intraperitoneal chemotherapy. However, the incidence of neutropenia and intra-abdominal abscess were significantly higher after surgery and adjuvant intraperitoneal chemotherapy when compared with surgery alone (HR 4.33, p=0.007 and HR 2.37, p=0.004).[28]

In a recent meta-analysis,[30] adjuvant intraperitoneal chemotherapy improved significantly 1-, 2-, and 3-year overall survival (p<0.0001) in patients with high-risk resected gastric cancer. This survival benefit was observed for both patients with serosal invasion and those with regional lymph node metastases. However, meta-analysis of the six randomized studies which reported 5-year overall survival suggests that adjuvant intraperitoneal chemotherapy may not improve long-term survival (HR 0.89, p=0.71). The efficacy of adjuvant intraperitoneal chemotherapy with respect to reduction of the peritoneal recurrence rate was considerable (HR 0.50, p<0.0001). While adjuvant intraperitoneal chemotherapy appeared to have no impact on the nodal recurrence rate, the incidence of haematogenous metastases was lower for the patients treated with intraperitoneal chemotherapy. The latter may be due to absorption of chemotherapeutic agents from the peritoneal cavity and subsequent exposure of micro-metastases, especially in the liver, to these drugs.

Similarly, meta-analyses which included only HIPEC as adjuvant intraperitoneal treatment for resectable high-risk gastric cancer demonstrated improved survival and decreased peritoneal recurrence risk when compared to surgery alone.[31,32] In a meta-analysis of 10 randomised trials[29], the overall survival rate increased with a factor 1.4 (p<0.00001) and the local recurrence rate decreased by 55% (p=0.001). Another meta-analysis[32] included 16 randomised trials and demonstrated a highly significant increase in 1-, 3-, 5- and 9-year overall survival (p<0.0007) and a similar decrease in risk of recurrence. The addition of HIPEC was not found to be associated with higher risks of anastomotic leakage, ileus, bowel perforation or myelosuppression, but it increased the incidence of abdominal pain. Since most of these HIPEC studies were conducted in Asia, the GASTRICHIP study has been designed and is ongoing to address the benefit of adjuvant HIPEC after gastrectomy with D2 lymphadenectomy in western patients with locally advanced gastric cancer.[33]

### Treatment of peritoneal carcinomatosis

The benefit of CRS and intraperitoneal chemotherapy in manifest peritoneal dissemination of gastric cancer remains controversial. Randomised trials of postoperative intraperitoneal chemotherapy for PC of gastric origin have not been conducted. The joint experience of 15 western centres in CRS and HIPEC for PC of gastric origin, comprising 150 patients, revealed an overall median survival of only 9.2 months and a 5-year survival rate of 13%.[34] In a recent French multi-centre study,[35] 81 patients underwent CRS and HIPEC. The 5-year overall and disease-free survival rates were 18% and 11%, respectively. All patients who were disease free after 5-years had had complete CRS of a low peritoneal tumour burden. In the first randomised trial on HIPEC for PC of gastric origin, 68 Chinese patients were allocated CRS with or without HIPEC.[36] While morbidity did not vary, HIPEC with mitomycin C and cisplatin improved overall survival (11.2 vs. 5.6 months, p=0.046). Synchronous (versus metachronous), complete CRS, ≥6 cycles of systemic chemotherapy and absence of serious adverse effects were independ-

ent predictors for better survival. More recently, in a second, very small, randomised trial[37] of 16 patients with established PC of gastric origin, a survival benefit was observed for gastrectomy, CRS, HIPEC and systemic chemotherapy when compared to systemic chemotherapy alone (median overall survival 11.3 vs. 4.3 months, p-value not provided). All patients surviving after one year had undergone complete CRS for a relatively low peritoneal tumour burden. In conclusion, the survival of patients with PC of gastric origin after CRS and HIPEC, although improved, remains considerably poor. CRS and HIPEC should be considered only in highly selected patients, i.e. for those with a low peritoneal tumour burden and for whom complete CRS is possible.

### Neoadjuvant bidirectional chemotherapy

A new prospect in the treatment of PC of gastric origin involves the application of neoadjuvant bidirectional (intraperitoneal and systemic) chemotherapy before CRS and HIPEC. Recently, a specialized Japanese centre reported on its experience with 194 patients.[38] Only the 152 patients who had negative peritoneal cytology after this bidirectional chemotherapy proceeded to undergo CRS and HIPEC. In a third of the patients, a major pathological response was observed. This strategy was performed with acceptable morbidity and mortality in this specialised centre. The median survival of the patients who proceeded to CRS and HIPEC was 15.8 months and the 2- and 5-year survival rates were 32% and 11%, respectively. The patients who had positive cytology after neoadjuvant treatment exhibited a 7.5 month median survival. Pathological response, low tumour burden and completeness of CRS were independent predictors for a better prognosis.

### Palliative treatment of ascites

Peritoneal carcinomatosis is often complicated by debilitating malignant ascites which portends a poor prognosis and also severely impairs quality of life. The treatment options include repeated paracentesis, diuretics and systemic chemotherapy, but none of them result in a permanent resolution of the ascites.[39]

HIPEC has been used to palliate refractory ascites in patients with PC originating from gastric cancer. Fujimoto et al.[40] and Yonemura et al.[41] had previously reported complete disappearance of ascites in patients who underwent HIPEC. More recently, series of laparoscopic HIPEC have been reported for palliating patients with intractable debilitating ascites from PC of gastric origin requiring repeated paracentesis.[42-44] Complete clinical regression of ascites and its related symptoms was achieved in the majority of patients without any major complications or mortality. A systematic review[45] identified 5 studies comprising 76 patients (37 with gastric cancer) treated by laparoscopic HIPEC for ascites. The authors reported that the procedure was successful in controlling ascites in 95% of cases. There were no major complications, while the incidence of minor complications was 7.6%.

An ongoing German study (PIPAC GA-01; NCT01854255)[46] is investing the clinical benefits of pressurised intraperitoneal chemotherapy (cisplatin and doxorubicin) in the form of an aerosol delivered by means of laparoscopy in patients with recurrent gastric cancer.

## FUTURE DIRECTIONS

In a recent systematic review of studies on intraperitoneal chemotherapy for gastric cancer reported between 2004 and 2010,[47] there were two randomised controlled trials, two case–control studies and ten observational studies. Methodological quality was rated as poor in 12 studies, with selection and observer bias apparent in most non-randomised cohorts. Studies were often small and varied in terms of intraperitoneal timing of chemotherapy, chemotherapeutic agents, treatment temperature, and the use of adjuvant therapies. Therefore, there is limited good-quality evidence to determine the role of intraperitoneal

chemotherapy in gastric cancer. Intraperitoneal chemotherapy in gastric cancer seems worthy of further appraisal. As the majority of trials were performed in Asia, it remains unclear whether the results can be extrapolated to western countries and vice versa. It is possible that perioperative intraperitoneal chemotherapy might be of greater benefit to western patients with more advanced disease and less extensive lymph node dissection. There is a need for larger randomised trials to be performed also on western populations, while the quality of trials must be improved, and studies must be conducted more uniformly to minimise bias and to aid comparison between centres.

## CONCLUSIONS

Adjuvant intraperitoneal chemotherapy after gastrectomy for locally advanced gastric cancer seems to be beneficial with regard to overall survival. HIPEC with or without early postoperative intraperitoneal chemotherapy, appears to be more effective than early postoperative intraperitoneal chemotherapy alone. The majority of studies has been performed in Asian countries. The results of a western ongoing randomised study on the benefit of adjuvant HIPEC after gastrectomy are eagerly awaited. The benefit of CRS and intraperitoneal chemotherapy in patients with manifest peritoneal dissemination of gastric cancer remains controversial. There is limited evidence that this multimodality treatment improves survival in selected patients with gastric PC, while outcome remains considerably poor. Adequate patient selection seems of utmost importance. Neoadjuvant bidirectional (intraperitoneal and systemic) chemotherapy seems promising, while intraperitoneal chemotherapy seems effective in palliative treatment of ascites in patients with gastric PC. It seems that there is a potential role of intraperitoneal chemotherapy in terms of improved overall survival and reduced risk of recurrence for patients with advanced gastric cancer. However, more well-designed prospective multi-institutional randomised trials, with a clearly defined protocol for concealed allocation, eligibility criteria, interventions and end-points are needed to define the role of intraperitoneal chemotherapy in gastric cancer.

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REVIEW

# The role of laparoscopy in the staging of gastric cancer
## A short review of the recent literature

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**ABSTRACT**

**Accurate staging has an important role in therapeutic decision-making for the successful management of advanced gastric cancer. Despite its significance, there is no single gold-standard algorithm for staging and a multimodality approach is followed. Laparoscopic staging of gastric cancer has been proven as an effective, minimally invasive, surgical technique, with increased rates of sensitivity and specificity, in comparison with imaging methods and laparotomy. Accompanied with peritoneal lavage and laparoscopic ultrasound, this method presents an improved accuracy in detecting radiologically unidentified metastases, peritoneal dissemination and even free intraabdominal cancer cells. Laparoscopic staging determines more clearly the state of gastric cancer, the proper therapeutic approach, decreasing the rate of unnecessary laparotomies and leading to lower morbidity. Furthermore, laparoscopy can be used as a second-look staging method (postoperatively and after chemotherapy) in order to indicate any downstage or upstage of the tumor. Current developments on this method (laparoscopic narrow-band imaging, real-time PCR) can easily detect even micrometastasis. To conclude, laparoscopic staging is a well-promising, safe, and useful tool for the successful management of gastric cancer, improving the 5-year survival rate.**

**KEY WORDS:** Laparoscopy, staging, advanced gastric cancer, peritoneal lavage cytology, recurrence, second-look laparoscopy.

## INTRODUCTION

Gastric cancer is the fourth most common cancer worldwide with more than 800,000 new diagnosed cases every year and it consists the second most usual cause of cancer-death.[1] Only 52% of patients with gastric cancer presents with potentially treatable disease as, 48% of all the patients presents with advanced stage at the time of diagnosis (with liver, distant and/or peritoneal metastases) with poor 5-year survival rate. Patients with gastric tumors undergo multimodality treatment and many efforts have focused on earlier detection, more accurate staging and more specific therapeutic approach in order to avoid unnecessary surgery.[2,3]

Currently, there is no single, gold-standard

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algorithm for staging of gastric cancer and a variety of preoperative staging techniques should be performed. However, these imaging methods usually miss to identify small peritoneal implants, which also, may not be detected during exploratory laparotomy.[4] Moreover, in up to 30% of all the patients with no preoperative diagnosis of metastases presents tumor lesions intraoperatively and the resection cannot improve the overall survival.[5] Except from endoscopic ultrasound (EUS), computerized tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET) and laparotomy, several newer developed techniques as well as diagnostic laparoscopy (DL), sentinel node mapping (SN) and narrow-band imaging (NBI) are coming in order to achieve a more accurate staging, which have increased the intraoperative staging accuracy.[6]

Staging laparoscopy (SL) is a minimally invasive procedure that was first used in 1990 for a great amount of malignancies and gastric cancer, as well.[7] This surgical technique seems to have higher overall accuracy in comparison with all the other staging methods. According to current literature data, the overall accuracy (85-98.9%) of SL presents sensitivity and specificity ranging from 64.3-94% and 80-100%, respectively, and avoiding laparotomies in 8.5-43.8% of all cases.[8] So, SL targets to early detect any tumor lesions, occult in preoperative staging, and to decrease the morbidity and mortality related with laparotomies.

## INDICATIONS

Many controversies exist about the proper patient selection for SL. According to the NCCN guidelines, SL should be performed for all the patients who had no preoperatively metastatic disease. In Western countries, up to 80% of the patients with gastric adenocarcinoma has advanced disease at the time of diagnosis so, SL may be necessary for all of these patients, regardless the exact tumor stage. On the other hand, in East countries, 60% of all the patients presents early stage disease so, SL is not necessary as, no metastasis is suspected.[9] According to the Society of Gastrointestinal and Endoscopic Surgeons (SAGES), SL is recommended for all the patients with advanced gastric adenocarcinoma (T3-T4) without distant metastasis, but not for patients with early gastric cancer (T1-T2). Furthermore, both the European Society for Medical Oncology (ESMO) and the NCCN recommend the use of laparoscopy in all patients considered to have resectable tumor.[10,11] Nowadays, all patients with gastric cancer type 4 or large type 3 (equal or larger than 8cm) without metastases are appropriate candidates for SL. Japanese National Cancer Center refers unexpected peritoneal metastasis in 40-60% of patients with T3-T4 tumors which were diagnosed as resectable by imaging methods.[12] Strandby et al. clearly states that, as far as peritoneal metastases is concerned, M-staging cannot be accurate without SL and it is strongly recommended for the accurate evaluation of cancer located on posterior gastric wall. Finally, SL should be performed by well-educated surgeons in laparoscopic surgery who can probably carry out therapeutic interventions when indicated.[13,14]

## LAPAROSCOPIC STAGING TECHNIQUE

SL is carried out under general anesthesia, with the patient in supine position. Three trocars (periumbilical, right and left quadrant) are usually used. Pneumoperitoneum is created with insufflation of $CO^2$ and an angled laparoscope $30^o$ is inserted via the umbilical port. The aim is to explore all the peritoneal surfaces (hemidiaphragams, stomach, liver, peritoneum, omentum, falciform ligament, small bowel mesentery, transverse mesocolon, paraaortic lymph nodes, pelvis), including exploration of the lesser sac (in posterior gastric tumors). SL targets to evaluate the tumor depth (T-staging), identify any nodal disease (N-staging) and detect peritoneal and/or liver metastases (M-staging).[8,15]

During SL, peritoneal washings should be obtained from right and left upper quadrant and

the pelvis. Cytology is carried out by aspirating ascitic fluid or after instilling 200ml of normal saline in absence of ascites. Positive peritoneal cytology (CY1) is not uncommon in gastric cancer and consists a marker of poor prognosis and a contradiction to perform curative resections, while neoadjuvant therapy should be seriously considered for downstaging.[10,16]

Moreover, SL combined with laparoscopic ultrasound (5-12 MHz) (LUS) can be used in order to explore more accurately intraabdominal organs (parenchymal liver metastases, gastrohepatic/periaortic lymph nodes) and tumor spread to the adjacent organs. LUS has proved to be useful in the assessment and detecting of small liver and lymph node metastases and a valuable tool in guiding frozen section biopsies.[10,15] Technically, it is initially placed over segment 8 of the liver and then, it is moved across the liver segments.[4] For patients with negative findings on SL, neoadjuvant chemotherapy and subsequent resection of tumor are offered after downstaging.

SL contradictions include gastric cancer complicated with obstruction, hemorrhage and perforation which require palliative therapy, multiple upper abdominal adhesions caused by previous surgeries as well as other anesthesia risk factors. Procedure-related complications are rare and the most common of these is urinary retention, postoperative bleeding, intraperitoneal organ injury and infections. No mortality has been reported.[9]

## ADVANTAGES IN LAPAROSCOPIC STAGING

SL has offered a great benefit to surgical oncology, according to patients and surgeons. The most important benefit of SL is that it can identify the presence of radiologically unidentified metastases in 13-57% of patients in order to achieve a R0 resection for gastric cancer.[15] Peritoneal lavage during laparoscopic staging can detect even free intraperitoneal cancer cells which consists an independent poor prognostic factor.[8] In comparison with exploratory laparotomy, SL reduces surgical morbidity, mortality, hospitalization, recovery time and time to initiation of appropriate systemic therapy. In addition, SL provides less intraoperative blood loss and less perioperative pain. Moreover, by using this accurate modality, we can avoid unnecessary laparotomies to one third of the patients with newly diagnosed gastric cancer so, they do not result in increased rate of morbidity.[10]

Moreover, neoadjuvant chemotherapy has been introduced for locally advanced gastric cancer in order to improve the rate of R0 resection and survival. However, its role remains controversial because of the lack of sensitive staging methods.[17] Laparoscopy also offers a more accurate staging, leading to a beneficial use of neoadjuvant chemotherapy.

Despite the fact that SL seems to be used infrequently in older patients with gastric cancer, it can be beneficial to this population group because of the higher risk of postoperative complications from laparotomy.[18] Finally, laparoscopy can also directly visualize small peritoneal tumor sites in regions that are difficult to be evaluated in laparotomy and offers safety, tissue biopsy, peritoneal washing for detection of free cancer cells and palliative by-pass (gastro-jejunostomy), when obstruction is caused by gastric cancer.

## SECOND-LOOK SL IN RECURRENCE DISEASE

Tumor recurrence is possible to appear in case of treatment failure, even in cases with achieved R0 resection. The most common recurrence pattern is peritoneal dissemination followed by retroperitoneal lymph nodes and hematogenous metastases.[14] An early detection of this recurrence results in better survival rates. CT is the standard imaging method that is currently used to assess the gastric tumor recurrence but its reported accuracy is about 60-70%.[2,19] New surgical opinions introduce a second-look laparoscopy as suitable technique for identifying recurrence.[1] Ishigami et al. study

supports that in patients with total resection, a second-look laparoscopy can confirm the clear excision margins. Also, in patients who receive chemotherapy for peritoneal metastasis (P1) or CY1, all metastatic lesions cannot be identified by imaging methods and a second-look laparoscopy should be performed for more accurate staging.[20] Metastatic disease, which cannot be detected by imaging methods, can be developed in 7% of patients who received neoadjuvant chemotherapy. This disease has a poor rate of survival and a few studies support repeat laparoscopic staging with peritoneal washings to select patients from this group with probably treatable tumor.[3]

The risk of tumor port-site recurrence is about 9% and remains a major concern among laparoscopists. Throughout literature, many factors have been reported as risky for causing port-site metastases such as $CO^2$ diffusion, low surgeon experience, and inappropriate tumor handling, direct electrostatic cell adhesions to ports, metallic trocar material and hematogenous spread.[21] Many studies claim that metastases at the trocar site are more likely shown to patients with widespread carcinomatosis at the time of staging.[10] Moreover, many surgeons remain suspicious to the role of laparoscopy as they claim that the $CO^2$ gas pneumoperitoneum can cause dissemination of cancer cells.

## SL VERSUS IMAGING AND OTHER TECHNIQUES

Currently, CT with multiplanar reconstructions of thorax, abdomen and pelvis is the standard preoperative imaging modality for gastric cancer. However, it is reported that CT misses up to 45% of <5mm peritoneal and liver nodes and its ability to determine the TNM stage correctly is less than 80-90%. A new developed CT technique, contrast-enhanced CT (CECT) presents an improved imaging accuracy. However, the study of Kabroo et al. reported an overall accuracy of CECT for T-staging about 74%, with sensitivity of 65% and specificity of 79%, in contrast with laparoscopic staging which presented increased rates (81%, 76% and 86%, respectively) with a mild benefit on N-staging.[6,18] The sensitivity of abdominal US to identify peritoneal metastases is estimated lower than 9% while, EUS has 88% sensitivity and 99% specificity for T staging but, it cannot detect peritoneal and liver metastases and is mainly useful for early stages in order to identify the degree of gastric wall invasion.

PET and CT are more sensitive for M-staging than the other conventional imaging techniques. However, PET has poor sensitivity (50%) for detecting peritoneal metastases and increases the administration of radiation. It is also reported to have various sensitivity (21-40%) and specificity (73-89%) in lymph node staging but, 67% of sensitivity and 97% of specificity in detecting distant metastases. The major disadvantage of PET scan is the increased rate of false-negative results so; a great amount of patients can be led to unnecessary laparotomy. MRI presents higher accuracy in T-staging (83%) and similar one in N-staging (53%) with CT and PET. Newly developed MRI, diffusion weighted MRI (DW-MRI), is mainly studied for solid tumors, with a small amount of trials focused on its role for the staging of gastric cancer.

Double contrast-enhanced US (CEUS) consists a new development of US which uses intravenous and intraluminal contrast for better visualization. Zheng et al. showed that this method was similar with EUS in tumor depth invasion (CEUS 77.2% versus EUS 74.7%) and superior in N-staging (CEUS 78.4% versus EUS 57.4%), according to its accuracy. Magnifying endoscopy with narrow-band imaging (ME-NBI) is also developed for T-staging with multi-detector row CT and its accuracy is reported about 80-90%. It can successfully visualize all the vessels along the gastrointestinal tract and mucosa surface so; it can differentiate mucosal from submucosal cancer.[6,18] However, its accuracy for N-staging is about <64% with 74% sensitivity and 80% specificity.

Another known invasive technique for staging of gastric cancer is SN which can identify clinically undetectable lymph node metastasis. The most common method that is used is dual-tracer one with radioactive colloid and blue dye. A current meta-analysis reported increased rates of sensitivity, specificity and accuracy for this invasive method (76.9%, 90.3% and 92%, respectively).[6] Although non-invasive imaging modalities have been developed, laparoscopic staging is proven to be more sensitive in detecting intraabdominal metastases, nodal involvement, liver and peritoneal dissemination, even micrometastasis, as it offers direct visualization, combined with peritoneal lavage cytology and laparoscopic ultrasound. Stell et all stated that the accuracy of laparoscopic staging was superior to CT and US in identifying peritoneal (94%), hepatic (99%), and nodal metastases (65%).[22]

## NEW TECHNIQUES IN LAPAROSCOPIC STAGING

Photodynamic diagnosis using oral 5-aminolevulinic acid (ALA) detected by fluorescence light (400nm) seems to improve the detection sensitivity of laparoscopic staging for peritoneal metastases. ALA- fluorescence can be detected to all gastric tumors on serosa and peritoneum, but not to other sites because light cannot penetrate these tissues.[23] Kishi et al. compared the sensitivity of 5-ALA phodynamic diagnosis in advanced gastric cancer with conventional white light and found that 5-ALA offers increased rates of tumor identification (72% versus 39%). Murayama et al reported that it has higher accuracy than conventional one in staging (100% versus 85.7%), Both these studies showed that it is a safe and effective choice for the staging of gastric cancer.[6,23]

Since the last years, laparoscopic narrow-band imaging (NBI) has been developed for the detection of peritoneal metastases in gastric cancer. This technique seems to be more accurate and sensitive for the identification of dilated micro-vessels than the conventional laparoscopic white-light staging. NBI is an endoscopic method which uses 415 and 540nm light in order to visualize vascular lesions. Its sensitivity depends on the different color that vessels take according to their depth.[7]

Finally, reverse transcriptase polymerase chain reaction (PCR), real-time PCR and immunohistochemistry combined with laparoscopy is currently combined with laparoscopy for the staging of gastric cancer which can easily detect micometastasis.[6]

## CONCLUSIONS

Even with the most developed imaging techniques, complete staging accuracy (100%) has not been achieved yet. SL is appeared as a simple, safe, minimally invasive procedure, well-tolerated and accurate in detecting peritoneal metastasis missed by conventional imaging techniques. The role of laparoscopy seems to be significant in the management of gastric cancer as the choice of appropriate treatment is based on the exact determination of the tumor stage. SL combined perioperatively with LUS and peritoneal lavage cytology additionally improves the staging accuracy. Because of its higher accuracy rates, potentially, laparoscopic staging can lead to downstage or upstage so, is truly significant in decision-making progress for appropriate treatment of gastric cancer. Surgeons should always consider performing SL before initiating unnecessary laparotomies to patients with advanced gastric cancer.

### Abbreviations

NCCN: National Comprehensive Cancer Network; EUS: Endoscopic ultrasound; CT: Computerized Tomography; MRI: Magnetic Resonance Imaging; PET: Positron Emission Tomography; DL: Diagnostic Laparoscopy; SN: Sentinel Node mapping; NBI: Narrow Band Imaging; SL: Staging laparoscopy; SAGES: Society of Gastrointestinal and Endoscopic Surgeons; ESMO: European Society for Medical Oncology; CY1:

positive peritoneal cytology; LUS: Laparoscopic Ultrasound; US: Ultrasound; CECT: Contrast-Enhanced CT; DW-MRI: Diffusion Weighted MRI; CEUS: Contrast-Enhanced US; ME-NBI: Magnifying Endoscopy with NBI; ALA: 5-aminolevulinic acid; PCR: Polymerase Chain Reaction

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REVIEW

# The perspectives of sentinel lymph node biopsy in gastric cancer

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**ABSTRACT**

**In the era of minimally invasive surgery and the increasing interest in patients' quality of life, the traditional surgical approach to resectable gastric cancer, constituting of subtotal or total gastrectomy and D2 lymph node dissection, is debatable for patients suffering from early gastric cancer, as the vast majority of them (more than 80%) have no lymph node involvement. In these patients, the application of sentinel lymph node mapping and biopsy could diagnose those with absence of lymph node metastases, thus leading to function-preserving gastrectomy and preservation of quality of life. Tracers that can be used to detect sentinel lymph nodes include dyes and radioactive colloids. Nowadays, the combination of a dye and a radioisotope consists the most reliable method to identify sentinel nodes. However, the detection and dissection of sentinel lymph nodes is not enough if it is not accompanied by a reliable intraoperative method of assessing their metastatic status. Despite the application of newer, more sensitive histological techniques, hematoxylin and eosin staining continues to be the standard method of assessing sentinel lymph node status.In the absence of sentinel lymph node metastases, an open or laparoscopic function-preserving surgery, such as wedge resection, segmental gastrectomy, pyloric-preserving gastrectomy and proximal gastrectomy could be a safe option for patients with early-staged gastric cancer. However, well-planned prospective trials are needed to confirm the oncological safety and effectiveness of all these function-preserving surgical approaches.**

**KEY WORDS:** Early gastric cancer; sentinel lymph node biopsy; lymphatic basin; function-preserving gastrectomy; quality of life

## INTRODUCTION

In the era of minimally invasive surgery and the increasing interest in patients' quality of life, the traditional surgical approach to resectable gastric cancer, constituting of subtotal or total gastrectomy and D2 lymphadenectomy, is debatable for the cases of early gastric cancer. More than 80% of cases with early gastric cancer, meaning T1 or T2 tumors, have no lymph node involvement. As a consequence these patients probably undergo unnecessary major operations, which affect their quality of life as they are accompanied by significant morbidity due to late-phase complications, such as significant weight loss, anemia, dumping

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syndrome and functional bowel disorders. Theoretically this subgroup of gastric cancer patients could undergo an oncologically safe function-preserving gastrectomy with limited lymphadenectomy to prevent late post-gastrectomy complications. The idea is very attractive; however a major questions rises: is there any way to recognize those patients with early gastric cancer that are candidates for a more conservative treatment? In other words, how can we identify patients' nodal status without proceeding to extended lymphadenectomy? Fortunately, melanoma and breast cancer show the way; the application of sentinel node biopsy in both these malignancies has dramatically changed postoperative morbidity as it significantly reduced the rate of many useless extended operations.[1,2] In the same way, the application of sentinel node mapping and biopsy in gastric cancer could diagnose patients with the presence or absence of lymph node metastases and lead to extended or function-preserving gastrectomy, respectively. Recently, a prospective multicenter clinical study conducted by the Japan Society of Sentinel Node Navigation Surgery showed that the sentinel node concept is feasible in gastric cancer and could change the current surgical approach to a specific subgroup of gastric cancer patients.[3]

## CANDIDATES FOR SENTINEL NODE BIOPSY

Only patients with early-stage gastric cancer are considered potential candidates for sentinel node biopsy. More specifically, the application of the method should be restricted to patients with clinical T1 or T2 tumors, primary lesion less than 4 cm in greatest diameter and clinically negative lymph nodes.[4]

## TECHNIQUES FOR SENTINEL NODE MAPPING

Tracers that can be used to detect sentinel lymph nodes include dyes and radioactive colloids. The most commonly used dyes are isosulfan blue, patent blue violet and indocyanine green, while technetium 99m tin colloid is the most frequently preferred radioisotope.[5] Dye facilitates the intraoperative visualization of the sentinel nodes as well as the lymphatic vessels that drain lymph from the gastric wall to the nodes. On the other hand radioisotope permits the identification of the radioactivity of lymph nodes through gamma probe, making this method extremely necessary in laparoscopic approach and in the presence of excess intraperitoneal fatty tissue. For both these reasons, most authors believe that the combination of a dye and a radioisotope consists the most reliable method to identify sentinel nodes. It should be noted that, though blue dyes are generally considered more prevalent than indocyanine green in sentinel node mapping, the last one is the most frequently used dye nowadays, especially in Japan, due to adverse and more specifically allergic reactions caused by the blue dyes.[6] Fortunately, the problem with the reduced sensitivity of indocyanine green for detecting sentinel lymph nodes has been significantly reducedduring the last 10 years bythe development and application of new-sophisticated fluorescence systems, such as the infrared ray electronic endoscopy (Olympus Optical, Tokyo, Japan), the HyperEyeMedical System (Mizuho Medical, Tokyo, Japan) and D-light P System (Karl Storz, Tuttlingen, Germany).

The radioisotope is endoscopically injected into the 4 quadrants of the submucosal layer around the primary tumor the day before surgery. The same technique is used to inject the dye; however, the injection of the dye is performed intraoperatively and the stained lymphatic vessels and nodes are identified with naked eyes in less than 15 minutes.[7]

At the beginning of the application of sentinel lymph node in gastric cancer, it was believed that the identification and dissection of the sentinel lymph nodes would be sufficient to assess lymph node status, as it happens in cases of breast cancer and melanoma. However, the complicated gastric lymphatic flow and the phenomenon of skip

metastasesmade the majority of the researchers doubt whether pick-up method was appropriate for sentinel lymph node biopsy in gastric cancer.[8] On the other hand, Miwa et al who underwent the first multicenter clinical study of sentinel lymph node mapping in gastric cancer, proposed the concept of "sentinel lymphatic basin" for gastric cancer in 2003.[9] Interestingly, 10 years later Miwa's concept was confirmed by the results of the multicenter trial conducted by the Japan Society of Sentinel Node Navigation Surgery[3] which showed that from the four patients who had false negative sentinel lymph node biopsy results, the three had metastases in non-sentinel nodes inside a zone containing stained lymph nodes and lymphatic vessels, a zone called lymphatic basin. These findings led to the transition from the "sentinel lymph node concept" to the "lymphatic basin concept", which is nowadays the recommended method for sentinel lymph node retrieval.[4,10,11] The lymphatic basins of stomach are five and follow the five main arteries that supply blood to the stomach: the left gastric artery, the left gastroepiploic artery, the right gastric artery, the right gastroepiploic artery and the posterior gastric artery.[12]

## METHODS OF ASSESSING SENTINEL LYMPH NODE STATUS

The detection and dissection of sentinel lymph nodes is not enough if it is not accompanied by a reliable intraoperative method of assessing their metastatic status. The conventional approach uses hematoxylin and eosin staining for the histological detection of metastases in gastric sentinel lymph nodes. The problem with this classic staining technique is its variable range of accuracy in terms of identifying node metastases.[13] The application of newer, more sensitive histological techniques, including immunohistochemical staining and reverse transcription-polymerase chain reaction (RT-PCR), has dramatically increased the detection rate of metastases.[14] Nonetheless, it should be kept in mind that the vast majority of metastases that are diagnosed by these methods, and are misdiagnosed by the hematoxylin and eosin staining, are micrometastases.[15] Since the clinical and prognostic role of micrometastases in early gastric cancer is still unclear, the significance of their identification is currently questionable. For this reason and due to other drawbacks of the new histological methods (cost, time till the diagnosis, unavailability in many centers), hematoxylin and eosin staining with multiple slices continues to be the standard method of assessing sentinel lymph node status.

## TREATMENT OPTIONS IN THE ERA OF SENTINEL LYMPH NODE BIOPSY IN EARLY GASTRIC CANCER

In case metastases are detected in the sentinel lymph nodes, we should proceed to formal gastrectomy, meaning subtotal or total gastrectomy, according to the location of the primary tumor, plus D2 lymph node dissection. However, in the absence ofsentinel lymph node metastases, an open or laparoscopic function-preserving surgery, such as wedge resection, segmental gastrectomy, pyloric-preserving gastrectomy and proximal gastrectomy could theoretically be a safe option for patients with early-staged gastric cancer.[5,16] At least one multicenter prospective study is in progress that investigates the curability and patients' quality of life after sentinel lymph node biopsy and function-preserving gastrectomy.[4] Another option, at least for cT1 early gastric tumors, could be (laparoscopic) sentinel lymph node biopsy, followed by endoscopic mucosal resection or endoscopic submucosal dissection in case of negative sentinel lymph nodes.Finally, the role of other minimally invasive techniques that have been recently developed, such as laparoscopic local resection, assisted by endoscopy (CLEAN-NET) and non-exposed endoscopic wall-inversion surgery (NEWS) is very promising for the treatment of early gastric cancer;[17,18] however well-planned prospective trials are needed to

study the oncological safety and effectiveness of all these minimally invasive approaches.

## CONCLUSIONS

The concept of sentinel lymph node biopsy in early gastric cancer with clinically negative lymph nodes is very attractive, as its application could lead to function-preserving surgery and improvement of the quality of life of a significant proportion of patients. The first results, especially after the application of sophisticated methods and techniques to accurately detect sentinel lymph nodes and assess their metastatic status,look very promising; however,no definite conclusion can be drawn before the completion of prospective studies that are in progress and investigate this specific topic.

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REVIEW

# D3 gastric resection
## Current practice and future perspectives

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**ABSTRACT**

**Surgery remains the main treatment for gastric cancer. Gastric resection should include not only the primary tumor but also the locoregional lymph nodes. In Western countries, D1 lymphadenectomy (i.e., removal of perigastric lymph nodes) is usually performed. Japanese surgeons first introduced the D2 gastrectomy (i.e., removal of lymph nodes along the three branches of the coeliac axis besides perigastric lymph nodes) in the 1960s and it is nowadays considered to be a safe operation. Since the 1980s, gastrectomy with more radical lymphadenectomy (D3; removal of paraaortic lymph nodes besides lymph nodes harvested in D1 and D2 type lymphadenectomy) has been conducted at specialized centers in Japan. Yet, the optimal extent of regional lymphadenectomy is still under debate. The aim of this review is to comprehensively address the effect of D3 gastrectomy on clinical outcome. Herein a review of clinical trials comparing D3 gastrectomy with D2/D1 gastric resection is depicted. Existing evidence does not support the superiority of D3 versus D2 lymphadenectomy since it is not associated with a survival advantage. Gastrectomy with D2 lymphadenectomy should be currently considered the standard treatment for localized, resectable gastric cancer. However, further clinical trials are necessary to explore the relationship between the therapeutic effect of lymphadenectomy and that of adjuvant and neoadjuvant chemo (radio) therapy. The role of sentinel node biopsy-guided lymphadenectomy needs to be defined. Finally, the comparison between D3 and D2 lymphadenectomy has so far been performed mainly in Asian patients, which calls for analogous comparisons in different ethnic groups.**

**KEY WORDS:** gastric cancer, lymph nodes, surgery, gastrectomy, lymph node excision, lymphadenectomy

## BACKGROUND

Gastric carcinoma represents the fifth most frequently diagnosed cancer and the third leading cause of death from cancer worldwide.[1] Surgery remains the only treatment that may lead to cure or long-term survival when used on its own.[2,3] It is widely accepted that gastric resection should include not only the primary tumor but also the locoregional lymph nodes (LNs), as these may harbor metastatic deposits. Yet, the optimal extent of regional lymphadenectomy is still under debate.

Removal of a wider range of LNs by extended LN dissection is expected to increase the prospect for cure by reducing the locoregional recurrence rate. On the other hand, if distant micrometastases have already been developed or if no LNs are invaded, such resection might be extraneous and hazardous, since the more extended the surgery,

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the greater the risk of operation related morbidity and mortality.

The aim of this review is to comprehensively address the issue of gastrectomy with more radical extended lymphadenectomy (D3 gastric resection) on the clinical outcome of patients with primary resectable carcinoma of the stomach.

## NOMENCLATURE

The complex LNs of the stomach have been arranged into a very practical classification by the Japanese Gastric Cancer Association (JGCA).[4] Thus, 16 different LN compartments (stations) are identified draining the stomach. These LN stations are classified into three groups that correspond to the location of the primary tumor and reflect the risk of harboring metastases (Table 1). Most perigastric LNs (stations 1–6) are defined as group N1, whereas the nodes along the left gastric (station 7), common hepatic (station 8), splenic (station 11), and proper hepatic (station 12) arteries and along the celiac axis (station 9) are defined as group N2 (Figure 1). Slight modifications of this schedule arise depending on the location of the primary tumor. For example, the LNs at the splenic hilum (station 10) also belong to group N2 when the tumor lies in the proximal stomach. The paraaortic LNs (station 16) are classified as group N3.

- D0 type lymphadenectomy: incomplete resection of perigastric lymph nodes
- D1 type lymphadenectomy: only lymph nodes strictly adjacent to the stomach (also known as perigastric lymph nodes) are removed during surgery.
- D2 type lymphadenectomy: in addition to perigastric lymph nodes, lymph nodes located along the three branches of the coeliac axis (i.e., left gastric artery, splenic artery and hepatic artery) are removed during surgery.
- D3 type lymphadenectomy: in addition to lymph nodes harvested in D1 and D2 type lymphadenectomy, lymph nodes located around the aorta (also known as para - aortic lymph nodes) are removed during surgery.[5]

## RATIONALE FOR D3 GASTRIC RESECTION

Japanese surgeons first introduced the D2 gastrectomy in the 1960s and it is nowadays considered to be a safe operation.[6] Since the 1980s, gastrectomy with more radical extended lymphadenectomy (D3; superextended lymphadenectomy) has been conducted at several specialized centers in Japan reasoning that the tumor spreads systematically through lymphatic channels from the stomach.[7-11]

Thus, more extended lymph node dissection could offer patients advanced probability of survival by two discrete mechanisms. First, more radical lymphadenectomy would lead to a more precise disease staging, which could improve survival by recognizing patients with high risk of recurrence who can benefit most from adjuvant therapy.[12] Second, removal of more lymph nodes should enhance the probability of removing microscopic metastatic deposits which are responsible for disease recurrence.[12]

The incidence of microscopic metastases in the paraaortic nodes was reported to be 6% to 33% in advanced gastric cancer.[10] Gastrectomy with super-extended lymph node dissection has been reported to lead to 5 year survival up to 12% to 23% for these patients. Yet, the issue of D3 superextended lymphadenectomy in gastric cancer patients had not been evidence-based addressed, until several randomized clinical trials comparing D3 gastrectomy with D2/D1 gastric resection were conducted.

## REVIEW OF CLINICAL TRIALS COMPARING D3 GASTRECTOMY WITH D2/D1 GASTRIC RESECTION

### D3/D1

A single-institutional trial that was carried out between 1993 and 1999 showed a statisti-

**Table 1.** Lymph node stations draining the stomach.

| | |
|---|---|
| No. 1 | Right paracardial LN |
| No. 2 | Left paracardial LN |
| No. 3a | LN along the left gastric vessels |
| No. 3b | LN along the right gastric vessels |
| No. 4sa | LN along the short gastric vessels |
| No. 4sb | LN along the left gastroepiploic vessels |
| No. 4d | LN along the right gastroepiploic vessels |
| No. 5 | Suprapyloric LN |
| No. 6 | Infrapyloric LN |
| No. 7 | LN along the left gastric artery |
| No. 8a | LN along the common hepatic artery (anterosuperior group) |
| No. 8b | LN along the common hepatic artery (posterior group) |
| No. 9 | LN along the celiac artery |
| No. 10 | LN at the splenic hilum |
| No. 11p | LN along the proximal splenic artery |
| No. 11d | LN along the distal splenic artery |
| No. 12a | LN in the hepatoduodenal ligament (along the hepatic artery) |
| No. 12b | LN in the hepatoduodenal ligament (along the bile duct) |
| No. 12p | LN in the hepatoduodenal ligament (behind the portal vain) |
| No. 13 | LN on the posterior surface of the pancreatic head |
| No. 14v | LN along the superior mesenteric vein |
| No. 14a | LN along the superior mesenteric artery |
| No. 15 | LN along the middle colic vessels |
| No. 16a1 | LN in the aortic hiatus |
| No. 16a2 | LN around the abdominal aorta (from the upper margin of the celiac trunk to the lower margin of the left renal vein) |
| No. 16b1 | LN around the abdominal aorta (from the lower margin of the left renal vein to the upper margin of the inferior mesenteric artery) |
| No. 16b2 | LN around the abdominal aorta (from the upper margin of the inferior mesenteric artery to the aortic bifurcation) |
| No. 17 | LN on the anterior surface of the pancreas head |
| No. 18 | LN along the inferior margin on the pancreas |
| No. 19 | Infradiaphragmatic LN |
| No. 20 | LN in the esophageal hiatus of the diaphragm |
| No. 110 | Paraesophageal LN in the lower thorax |
| No. 111 | Supradiaphragmatic LN |
| No. 112 | Posterior mediastinal LN |

LN= lymph nodes

cally significant survival benefit of D3 over D1 gastrectomy.[13,14] Of 221 patients, 111 patients were randomly assigned to D3 surgery and 110 patients were randomly assigned to D1 surgery. Overall 5-year survival was significantly higher in patients who underwent D3 surgery than in those

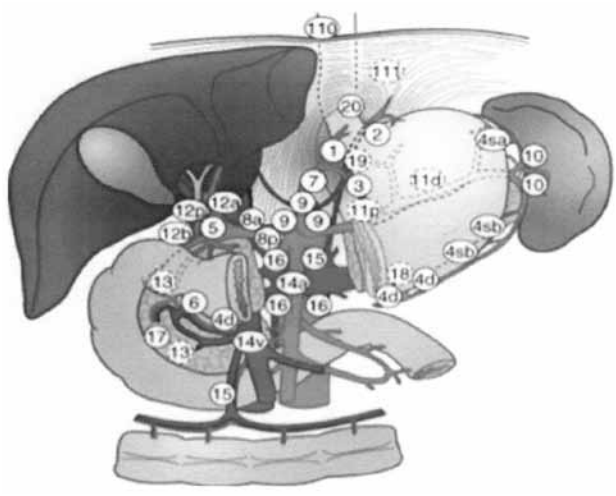

**Figure 1.** Lymph node stations.

who underwent D1 surgery (59.5% vs. 53.6%; p=0.041). Taken as a whole, 215 patients who had R0 resection had recurrence at 5 years (50.6% for D1 surgery and 40.3% for D3 surgery; p= 0.197). Five-year disease specific survival was significantly higher in patients assigned to D3 surgery than in those assigned to D1 surgery (64.9% vs. 58.5%; p=0.044; Hazard Ratio (HR), 0.69).

Yet, another small-scale randomized controlled trial *(*RCT) was conducted in Hong Kong between 1987 and 1991, which randomized 55 patients to either D1 or D3 gastrectomy.[15] D3 patients had more extended operative times, greater transfusion needs, lengthier hospital stays, and more subphrenic abscesses than D1 patients, while one patient in the D3 group died from postoperative complications. Overall survival was superior in the D1 group (p= 0.07).

### D3/D2

A RCT comparing D2 gastrectomy with D3 lymphadenectomy was conducted by the Japanese Clinical Oncology Group (JCOG) between 1995 and 2001.[16] A total of 523 patients with curable T2b, T3, or T4 gastric cancer were randomly allocated to D2 (263 patients) or to D3 lymphadenectomy (260 patients). D3 lymphadenectomy had longer operation time and more blood loss than D2. The morbidity for the D3 lymphadenectomy group was higher than that for the D2 group (28.1% and 20.9%, respectively), but the difference was not statistically significant (p=0.067). On the whole, four hospital deaths were reported (0.8%), 2 patients in each group (p= 0.99). The 5-year overall survival after D3 lymphadenectomy was not significantly better than that after D2 lymphadenectomy (D2, 69.2% and D3, 70.3%; HR, 1.03; 95% Confidence Interval (CI), 0.77–1.37). This study concluded that prophylactic D3 lymphadenectomy should not be carried out for curable gastric cancer.

Another RCT comparing D2 with D3 lymphadenectomy was conducted between 1995 and 2002.[17,18] A total of 269 patients were randomized, with 135 patients submitted to D2 dissection and 134 patients submitted to D3 lymphadenectomy. Postoperative morbidity was significantly higher in the D3 lymphadenectomy group (39%) than in the D2 group (26%; p=0.023). Hospital mortality was 0.7% in the D2 group and 3.7% in the D3 lymphadenectomy group (p=0.12). The overall 5-year survival was 52.6% for the D2 group and 55.4% for the D3 lymphadenectomy group; no survival benefit of D3 lymphadenectomy over D2 lymphadenectomy was revealed (p=0.801).

One more clinical trial compared D2 to D3 lymphadenectomy in Poland.[19] Of 275 patients enrolled, 141 patients were assigned to D2 and 134 patients were assigned to D3 lymphadenectomy. The morbidity rates were 27.7% for D2 and 21.6% for D3 lymphadenectomy (p=0.248). The postoperative mortality rates were 4.9% for D2 and 2.2% for D3 lymphadenectomy (p=0.375). In this study, D3 lymphadenectomy did not lead to increased morbidity and mortality, but evidence of survival benefits is lacking.

These three trials revealed that both D2 and D3 gastrectomy are safe surgical procedures, but D3 dissection should not be carried out for curable gastric cancer, because evidence of survival benefits remain to be analyzed.[20]

## DISCUSSION

Existing data does not definitely support the

routine use of D3 lymphadenectomy in patients with curable gastric cancer, as the survival advantage is uncertain. In addition, it is generally accepted that more extensive operations lead to increased morbidity. Therefore, practice guidelines addressing the best level of lymph node dissection used to be more estimation based than evidence-based.[21] Therefore, a meta-analysis was recently performed in order to address the question: Does more extended lymphadenectomy offer a survival benefit for patients submitted to surgery for gastric carcinoma?[5] Accordingly, three RCTs from Japan were included, comparing D3 lymphadenectomy to D2 lymphadenectomy.[18,22,23]

Meta-analysis of these three RCTs (n = 862) verified the lack of statistically significant association between the level of lymphadenectomy and overall survival (OS) (HR 0.99, 95% CI 0.81 to 1.21). Moreover no data were available for the D3 versus D2 lymphadenectomy in terms of disease-specific survival (DSS). Furthermore, only one RCT was available, demonstrating no significant effect of lymphadenectomy level on disease-specific survival (DFS) (HR 1.08, 95%, CI 0.83 to 1.42).[23] Finally, meta-analysis of these three RCTs did not confirm any significant difference in terms of postoperative mortality rate between D3 and D2 lymphadenectomy (Relative Risk (RR) 1.67, 95% CI 0.41 to 6.73).

## Current status of lymphadenectomy

Existing evidence does not support the superiority of D3 versus D2 lymphadenectomy since it is not associated with a survival advantage in comparison with D2 lymphadenectomy. Thus D3 lymphadenectomy is not at the present time recommended for patients with curable gastric cancer.[5,20]

Gastrectomy with D2 lymphadenectomy should be currently considered the standard treatment for localized, resectable gastric cancer. This type of lymph node dissection contributes to accurate staging and offers significant benefit in terms of DSS. Yet, in Western countries D2 lymphadenectomy is considered a recommended but not a required procedure. Nevertheless, removal of an adequate number of lymph nodes (at least 15) is univocally regarded as beneficial for staging purposes.[5,20] D2 lymphadenectomy should be performed without prophylactic pancreatectomy and splenectomy, since patients submitted to a modified D2 lymphadenectomy (i.e., without splenopancreasectomy) had equal survival results as those undergoing standard D2 lymphadenectomy (i.e., including splenopancreasectomy) but had lower morbidity and mortality rate.[24,25] Splenectomy is recommended only when spleen or hilum is involved.

## Suggestions for future research

The need for more research in this field is underlined. Thus, trials are necessary to explore the relationship between the therapeutic effect of lymphadenectomy and that of currently existing adjuvant and neoadjuvant chemo (radio) therapy. In effect, it is still uncertain whether medical treatments may substitute the potential therapeutic advantage of more extensive lymphadenectomy, as well as whether the therapeutic result of medical treatments may synergize with more extensive lymph node dissection.[26] Furthermore, the role of sentinel node biopsy-guided lymphadenectomy needs to be defined and may possibly result in improved management of patients with gastric cancer, the same as it does for melanoma and breast cancer patients.[27]

To end with, the comparison between D3 and D2 lymphadenectomy has up until now been performed mainly in Asian patients, which calls for analogous comparisons in different ethnic groups.

## Conflict of interest

The authors declare that they have no conflict of interest.

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REVIEW

# Open or laparoscopic gastrectomy for gastric cancer?

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## INTRODUCTION

Initially, laparoscopy was implemented in order to determine the operability of gastric cancer.[1] Kitano et al. reported the first laparoscopy-assisted distal gastrectomy (LADG) for curative purpose.[2] Currently there are three types of laparoscopic gastrectomy: the totally laparoscopic procedure, the laparoscopy-assisted procedure, and the hand-assisted laparoscopic procedure.

Laparoscopic surgery appears to offer multiple advantages including reduced postoperative pain, rapid recovery of gastrointestinal function and a shorter hospitalization. On the other hand, there are many questions to be answered especially with regard to the extent of lymph node dissection and long term outcomes.

The aim of this study is to perform an updated critical evaluation of recently published original studies to determine whether laparoscopic gastrectomy (LG) is a better overall alternative of open gastrectomy (OG). Our major focus is to compare parameters of LG and OG, such as operative time, blood loss, harvested lymph nodes, postoperative complications, length of hospital stay,hospital mortality and oncologic outcomes.

## EARLY GASTRIC CANCER

Several studies have been conducted to assess the results of laparoscopic gastrectomy in the treatment of early gastric cancer (EGC) with increased risk of lymph node involvement. LADG seems to be the most popular technique and is associated with significantly decreased intraoperative blood loss, shorter times to first pass flatus, earlier onset of oral intake, less need for post-operative analgesics, faster ambulation and shorter hospitalization. Moreover, LADG improves post-operative quality of life, but does not appear to differ in terms of post-operative morbidity compared to open distal gastrectomy (ODG).[3-5] Inokuchi et al[6] confirmed these outcomes in their 2015 meta-analysis, but also reported that LADG is associated with a significantly lower incidence of surgical site infection (n=1737; odds ratio [OR] 0.50, 95% confidence interval [CI] 0.29-0.85, p=0.01, $I^2$= 0%, and OR 0.46, 95% CI 0.24-0.88, p=0.02; $I^2$=0%).

In addition, it seems that there is no significant difference in perioperative mortality between LADG and ODG, which suggests that LADG can achieve a comparable short-term prognosis

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to that of ODG. Ultimately, the extent of laparoscopy-assisted lymphadenectomy is parallel to the open procedure, which is accompanied by similar disease-free and five-year survival rates in patients treated with either LADG or ODG.[7-9] A meta-analysis performed by Zeng et al[10] indicated that there was no significant difference in the cost of the operating room (standardized mean difference (SMD) =-0.31; 95 % CI -1.37 to 0.750 and in total hospitalization costs (SMD = -0.98; 95 % CI -2.21 to 0.26) between LADG and ODG.

Encouraging results were also observed in studies reporting on total laparoscopic gastrectomy (TLG) vs open total gastrectomy. Specifically, TLG was associated with better short-term outcomes and sufficient lymph node dissection. Xiao et al[11] in their recent meta-analysis found that TLG results in significantly lower intraoperative bleeding and increased number of harvested lymph nodes in comparison to LADG. However, there was no difference in operation duration, time to first flatus, length of postoperative hospital stay and morbidity.

## ADVANCER GASTRIC CANCER

Although there is no worldwide consensus, the current standard of treatment for advanced gastric cancer (AGC) in Asian high-volume centers is the modified D2 surgery with preservation of the distal pancreas and spleen unless they are involved. On the contrary, European and North American surgeons perform D1 surgery plus neoadjuvant chemotherapy with or without postoperative radiochemotherapy.[12-14]

The feasibility and safety of performing laparoscopic D2 lymph node dissection was initially confirmed in EGC patients before applying the technique to AGC. Indeed, there was no significant difference in lymph nodes dissected by either LADG or ODG.[15-17] Moreover, intraoperative bleeding and postoperative hospitalization were significantly lower in LADG than in ODG.[16]

Several studies were conducted to determine the feasibility of laparoscopic gastrectomy with D2 lymphadenectomy in AGC, since Uyama et al. introduced the technique.[18] No significant differences were reported between LADG and ODG in terms of reoperation incidence, postoperative mortality, the extent of lymphadenectomy, recurrence rates, three-year or five-year disease-free and overall survival rates.[19-21] However, the operation of LADG lasts longer than ODG.

## ELDERLY PATIENTS

Yasuda et al[22] and Mochiki et al[23] reported the feasibility of laparoscopy-assisted gastrectomy in elderly patients. Although older patients had a higher incidence of preoperative morbidities, the frequency of intraoperative and postoperative complications was not significantly different from their younger counterparts, when they were treated laparoscopically.[24-26] Moreover, Kunisaki et al[27] found no significant difference in overall or disease-specific survival between the two groups. Also, Mochiki et al[23] reported similar 5-year survival rates between older and younger patients when treated laparoscopically.

## OBESE PATIENTS

Only a few studies have been carried out to analyze the feasibility and safety of laparoscopic gastrectomy in obese patients.[28-33] Most of them are retrospective case-control studies comparing obese and non-obese patients treated with laparoscopy-assisted gastrectomy for gastric cancer. The reported results concerning operative findings and short-term outcomes are controversial.

Except from Kim et al,[30] all other researchers have shown that LADG for obese patients lasts longer than LADG for patients with a normal BMI. Furthermore, no significant differences in terms of blood loss were noted in any study between obese and normal patients when they were treated laparoscopically. On the contrary, in ODG, blood loss seems to be significantly greater in the obese

group than in the non-obese group.[31,33]

As far as postoperative morbidity and mortality are concerned, Noshiro et al[28] noted a delayed recovery of bowel activity and a higher rate of transition to open surgery for obese patients. However all others researchers found no significant differences between the two groups.

Finally, according to the majority of published papers on the topic, the number of retrieved lymph nodes does not differ statistically between obese and non-obese patients. However, Lee et al.[8] recently reviewed clinical data from 1,485 laparoscopy-assisted procedures for gastric cancer in 10 institutes and found that the number of lymph nodes harvested was significantly smaller in the high BMI group than in the low BMI group. According to the authors, this phenomenon may have been caused by difficulties in nodal dissection as well as isolation of lymph nodes from the retrieved soft tissue, during handling of a specimen, in obese patients.

## CONCLUSIONS

Recent evidence suggests that the short- and long-term outcomes of laparoscopic surgery for EGC and AGC are comparable to those of conventional open surgery. However, further Level 1 evidence is required to confirm the suitability of laparoscopic surgery for gastric cancer, as well as the appropriate indications for its use. The ongoing large-scale multicenter RCTs are expected to clarify the oncologic safety of laparoscopic surgery in the near future.

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REVIEW

# Tips and tricks in laparoscopic gastrectomy

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**ABSTRACT**

**Since Theodor Billroth performed the first successful gastrectomy for gastric cancer in 1881, there has been a rapid development in the field of laparoscopic surgery. These developments include the invention of new surgical tools as well as surgical techniques which allow maximizing the advantages of the totally laparoscopic gastrectomy over the conventional open technique. However, although the advantages of the laparoscopic approach are well-established, there are still some controversial issues among the different laparoscopic techniques where a consensus has yet to be reached. The purpose of this article is to demonstrate these differences, especially regarding the patient's position, the ways of ligating major blood vessels supplying the stomach, the method of constructing the esophagojejunostomy after total gastrectomy and the possibility of applying the ERAS protocols following a totally laparoscopic gastrectomy and to provide useful tips for every surgeon in order to decide between the advantages and disadvantages of these techniques.**

**KEY WORDS:** Laparoscopic, gastrectomy, subtotal, total

## INTRODUCTION

The recommended treatment of gastric cancer consists of a radical resection of the stomach with a free margin of 5 to 6 cm. Depending on the location of the tumor, the procedure of choice is either total or subtotal gastrectomy.[1,2] In the past decade, laparoscopic techniques have gained wide clinical acceptance in surgical practice.[3,4] This approach offers important advantages when compared with open surgery; reduced intraoperative blood loss, reduced postoperative pain and accelerated recovery, earlier return to normal bowel function with earlier resumption of oral intake, early discharge from hospital, and lower financial costs.[5-7] The purpose of this article is to provide helpful tips and tricks regarding the laparoscopic approach of the two above-mentioned procedures.

## TECHNICAL CONSIDERATIONS

The first stomach resection for cancer was performed by Jules Emile Pean in 1879. In 1881, Austrian surgeon Theodor Billroth performed a successful gastroduodenostomy in a 43-year-old woman with pyloric cancer. It was performed following partial gastrectomy.[8] In 1994, Kitano performed the first laparoscopic assisted distal gastrectomy (LADG) with a modified D1 lymph node dissection (D1 + Left gastric artery group and D1 + common hepatic artery group) for the treatment gastric cancer with high risk of lymph node metastasis. This demonstrated the utility of laparoscopic surgery for gastric malignant disease in the East with regard to feasibility of an oncologically ap-

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propriate laparoscopic lymphadenectomy. In 1996, Azagra et al. reported the first laparoscopic total gastrectomy for cancer. Azagra et al. from Belgium have been western pioneers in minimally invasive gastric resection for cancer, performing the first totally laparoscopic distal gastrectomy with Billroth II anastomosis for cancer in 1993 and the first reported laparoscopic total gastrectomy for cancer in 2001. Despite the relatively new advent of these techniques, there has been an aggressive approach to reporting series of patients undergoing laparoscopic resections for gastric cancers.

For both total and subtotal gastectomy the patient is placed in a supine position and 15° reverse Trendelenburg position is maintained. Generally, port placements are similar for total and subtotal gastrectomy. In some cases, minor adjustments are made depending on patient body habitus.

For laparoscopic gastrectomy, an infra-umbilical 10-mm camera port is placed. After a pneumoperitoneum of 12 mmHg is achieved, ports are placed at the right upper quadrant, right lateral side, left upper quadrant, and left lateral side of the abdomen under direct visualization. The surgeon and scope operator are located on the right side of the patient and an assistant is on the left side.[9] Alternatively, a split-leg table can be used and in such a case the surgeon stands between the patient's legs. The assistant is located on the left side of the patient and the scrub nurse on the right.

According to the Japanese gastric cancer treatment guidelines, extent of lymphadenectomy is decided based on clinical stage of the tumor and type of gastrectomy indicated. D1+ lymphadenectomy is indicated for cT1N0 tumors and D2 is indicated for cN+ or cT2–T4 tumors.[10] Regarding the feasibility and efficacy, there have been many major studies comparing D1+ and D2 dissection in laparoscopic and open gastrectomy for gastric cancer. The majority of them conclude that although the laparoscopic approach is a more time-consuming procedure, it seems to be slightly superior or similar to open gastrectomy in terms of postoperative recovery measures. Moreover, it has been associated with less intraoperative blood loss and shorter hospital stay, while it seems that there are no significant differences regarding postoperative complications, morbidity, mortality and the number of harvested lymph nodes. As a result, in spite of being a technologically-demanding and time consuming procedure, the laparoscopic approach is oncologically acceptable and offers some advantages over the open approach.[11-16]

In terms of ligation, coagulation and dissection, the Ultrasonic Harmonic Scalpel has demonstrated clinical and surgical benefits. To evaluate its use, a systematic review and meta-analysis of randomized controlled trials comparing the Harmonic scalpel to conventional techniques in gastrectomy for patients with gastric cancer showed that compared to conventional hemostatic techniques, the Harmonic scalpel demonstrated significant reductions in operating time (-27.5 min; $p<0.001$), intraoperative blood loss (-93.2 mL; $p<0.001$), and drainage volume (-138.8 mL; $p<0.001$). Results were numerically higher for conventional techniques for hospital length of stay, complication risk, and transfusions but did not reach statistical significance. Results remained robust to sensitivity analyses. This meta-analysis demonstrates the clear advantages of using the Harmonic scalpel compared to conventional techniques, with improvements demonstrated across several outcome measures for patients undergoing gastrectomy and lymphadenectomy.[17]

Other widely used means of ligation include energy-based devices such as the Ligasure, the Enseal tissue sealing system and the Caiman device as well as hemostatic clips such as titanium or Hem-o-lok clips. However, based on recent studies, it seems that there is no real winner between the above mentioned methods, leaving it up to every single surgeon to perform every procedure based on his own habits and instrument preferences. We prefer to ligate major vessels such as the left gastric artery using the combination of hemostatic clips and ligasure.

Digestive tract reconstruction after laparoscopic distal gastrectomy: The most common surgical procedure being Roux-en-Y reconstruction.

Small incision-assisted approaches were initially used. However, a totally laparoscopic side to side gastrojejunostomy on the anterior wall of the gastric remnant using laparoscopic staplers is easy to perform and has become the procedure of choice. The enterotomy and the gastrotomy can be closed either by sutures or by stapler. Regarding the jejonojejanostomy, it can be performed either laparoscopically or open through the small incision made to extract the specimen.

Digestive tract reconstruction after laparoscopic total gastrectomy: during the laparoscopic total gastrectomy, the exposure of the lower esophagus is more complete and surgical field is clearer, and the dissociation is more convenient. Small incision-assisted Roux-en-Y reconstruction is often preferred. This procedure is highly safe, easy to perform, time-saving, and economically affordable. Therefore, it has become the most commonly used reconstruction method. However, this procedure also has some limitations: it is often limited by the patients' body shape and the tumor condition. In patients with obesity, left hepatic hypertrophy, small costal angle, or high tumor location, the esophagus is expected to be divided at relatively high level. In such cases, the small incision-assisted reconstruction is often more difficult, and the incision often has to be extended to ensure the safety of the procedure. Therefore, in difficult cases, appropriately extending the small incision is particularly important to ensure the anastomosis safety. To avoid this limitation, in recent years we have adopted the completely laparoscopic esophagus-jejunum anastomosis, which has shown better surgical field, simpler operation, and higher safety. It may become the optimal digestive tract reconstruction method after laparoscopic total gastrectomy. The completely laparoscopic oesophagus-jejunum anastomosis can be performed using two different instruments: circular stapler or linear cutter & stapler.

The most challenging tasks during this procedure include the purse-string suture and the placement of the anvil. We prefer to divide only the anterior wall of the oesophagus, do half of the purse string suture, insert the anvil of the stapler and then complete the division of the oesophageal wall and the purse string suture. This approach is safer and more effective than the placement of an anvil after the complete transection of the esophagus followed by the purse-string suture, because it prevents the retraction of the esophageal stump into the mediastinum. Another method of performing esophagojejunostomy is the transorally-inserted anvil (OrVil™) technique, which inserts the stapler anvil through a transoral esophageal approach. A tube is connected with the central rod of the stapler. The tube is inserted in the esophagus and pulled out from the esophageal stump, and the anvil is placed under the guide of the tube by the anesthesiologist.[18] As the operator identifies the OrVil™ tube reaching the esophageal stump, a small hole is made on the esophageal stump. The tube is then extracted through the hole until the anvil reaches the esophageal stump. When the pre-tilted anvil is introduced into the mouth, the anesthesiologist should protect and confirm that the anvil is inserted through the upper esophageal sphincter under the laryngoscopic view. Then, the tube is disconnected from the anvil by cutting the connecting thread and removed from the abdominal cavity.[19] Another variation in the construction of the esophagojejunostomy is the anastomosis of the jejunum with a small remnant of gastric mucosa in the area of the gastroesophageal junction, which is left intentionally by the surgeon during the division of the esophagus. This technique provides more safety as it actually creates a gastrojejunostomy, however, it can only be performed when it is oncologically acceptable. The method we prefer to ensure a secure anastomosis is the laparoscopic placement of the anvil and the purse-string suture through a small incision in the esophageal wall before its complete transaction. This way, we minimize the risk of esophageal mucosa retraction due to high elasticity, thus creating a secure esophagojejunostomy.

Laparoscopic technique combined with the ERAS (Enhanced Recovery after Surgery) pro-

tocol enables a shorter hospital stay and a lower complication rate.[20] In 2014, K. Mortensen et al. published a comprehensive set of guidelines for enhanced recovery after gastrectomy for cancer.[21]

## CONCLUSION

Laparoscopic gastrectomy for gastric cancer is a complex procedure, which can be performed safely with the expected advantages of laparoscopic surgery. An important thing is education. As the number of laparoscopic gastric surgeries has increased rapidly, the importance of education for laparoscopic skills becomes higher.

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REVIEW

# Restoration of continuity of gastrointestinal system following subtotal gastrectomy
## Roux-en-Y or Billroth II

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**ABSTRACT**

**Restoration of continuity of the gastrointestinal system following a subtotal gastrectomy is still a controversial issue. The most commonly used techniques are Billroth II and Roux-en-Y. Billroth II, more formally Billroth's operation II, is an operation in which the greater curvature of the stomach is connected to the first part of the jejunum in a side-to-side manner. Roux-en-Y anastomosis is an anastomosis of the distal end of the divided jejunum to the stomach, with implantation of the proximal end into the side of the jejunum at a suitable distance usually more than 40cm below the first anastomosis. The bowel then forms a Y-shaped pattern. Both procedures have been associated with certain complications such as anastomotic leak, postoperative lack of appetite as well as weight loss, dumping syndrome, postprandial abdominal fullness, recurrent ulcer and gastric stump cancer. The majority of recent studies conclude that Roux-en-Y anastomosis is a safer and preferred procedure due to the lesser incidence of the above mentioned complications.**

**KEY WORDS:** gastrectomy, Roux-en-Y, Billroth II

The first stomach resection for cancer was performed by Jules Emile Pean in 1879. A year later, a Polish surgeon named Ludwik Rydygier performed gastroenterostomy for the management of peptic ulcer disease. Unfortunately, both of these attempts were unsuccessful. In 1881, Austrian surgeon Theodor Billroth performed a successful gastroduodenostomy in a 43-year-old woman with pyloric cancer. It was performed following partial gastrectomy. This procedure later came to be known as the Billroth I operation to differentiate it from the Billroth II operation, in which gastrojejunal reconstruction was performed following partial gastrectomy. In 1885, when Billroth encountered a patient with a large pyloric tumor, instead of performing gastroduodenostomy following partial gastrectomy, he performed gastrojejunostomy proximal to the growth as a bypass

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to alleviate the symptoms of gastric outlet obstruction as a first-stage procedure because of the poor general condition of the patient. A second-stage resection of the tumor was performed, and the terminal end of the stomach and proximal end of the duodenum were closed. This was described by von Hacker as Billroth II partial gastrectomy.

Billroth II gastrectomy has nowadays been associated with many early and late postoperative complications. The most important late postoperative complications which are the deciding factors in favor of Roux-en-Y over Billroth II is the alkaline gastritis and anastomotic ulcers which can lead to gastric stump cancer. Enterogastric reflux, achlorhydria, bacterial overgrowth, and H. pylori infection are the major factors involved in pathogenesis. The risk of stump carcinoma is time-dependent, usually occurring 10 years or longer after gastric resection. Patients with stump carcinoma typically present late in the course with more advanced disease. Operable tumors would require a total gastrectomy with Roux-en-Y reconstruction. The prognosis in these patients is generally poor.

In general surgery, a Roux-en-Y anastomosis, or Roux-en-Y, is a surgically created end-to-side anastomosis most commonly performed to remove a malignancy. In layman's terms, after this procedure food can go more directly into the small intestine. Unfortunately, the reduced time in the stomach means partially digested food goes into the small intestine, which tends to produce undesirable digestive problems. Typically, the surgical change is between stomach and small bowel that is distal (or further down the gastrointestinal tract) from the cut end.

The name Roux is derived from the surgeon who first described it (César Roux) and the stick-figure representation. Diagrammatically, the Roux-en-Y anastomosis looks a little like the letter Y. Typically, the two upper limbs of the Y represent (1) the proximal segment of stomach and the distal small bowel it joins with and (2) the blind end that is surgically divided off, and the lower part of the Y is formed by the distal small bowel beyond the anastomosis.

Roux en Y surgery can dramatically change food digestion dynamics, most of them negatively. One major change relates to digestion processes and the other major change to malabsorption deficits.

A common digestive result of Roux surgery is "dumping syndrome", a type of diarrhea in which the fecal matter is popcorn sized in appearance.

Next, nutritional factors are changed in Roux surgery. The first part of the intestine after the stomach is the small intestine, whose primary job is to absorb nutrients. Nutritional deficiencies can result from Roux surgery because every inch of the small intestine is vital for nutritional absorption, and many Roux surgeries result in the initial parts of the small intestine being bypassed by all or some of the food. All Roux surgeries result in a new stomach outlet, and that "open exit door" is the source of numerous problems

The Roux surgery creates a constantly open hole in the stomach bottom which allows undigested food to freely enter the small intestine. When that unusual format food contains a high liquid content or refined sugars (soda, beer, cake icing, carbohydrates, etc.) the intestine begins moving that food to the anus as quickly as possibly, creating dumping syndrome. Dumping continues until the offending foods in the small intestine are ejected from the large intestine and anus. With a normal intestine of about 30-feet, six or eight bowel movements are typically required, going from normal fecal compositions to watery.

Last, the "transit time" for food may be reduced, based on sugar content, fluid content and undigested foods. In other words, if the time from mouth to bowel movement is reduced, there is less time for the intestines to remove nutrients, again contributing to nutritional deficits and weight loss. Where weight loss was the primary objective, that may be acceptable. But for patients who have Roux surgery due to pyloric inflammation, stomach cancer, etc., weight loss can become a new chronic health problem.

## CONCLUSIONS

In conclusion, there have been many major recent studies comparing the results and the post-operative complications of Billroth II and Roux-en-Y. Following the results of the above mentioned studies we came to the conclusion that although RY reconstruction may have some complications, these are due to the nutritional habits of the patient. Specifically, the consumption of large amounts of food which is rich in sugar and fat is the main cause of diarrhea and dumping syndrome after RY reconstruction. However, this is not the case with BII reconstruction, where the complications are the result of the technique itself. Most importantly, bile and pancreatic fluid reflux is the main cause of alkaline gastritis which leads to gastric stump cancer. Moreover, most studies show that patients with RY reconstruction complained significantly less of reflux symptoms and had significantly reduced reflux gastritis and esophagitis. Quality of life was significantly improved in patients with RY reconstruction compared with patients with BII reconstruction. Last but not least, in every major study that has been conducted until now, it is shown that the only way to alleviate a patient from the symptoms caused by a BII complication is the transformation of BII into a RY anastomosis.

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REVIEW

# Current surgical management of hepatic metastases from gastric cancer

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**ABSTRACT**

**Hepatic metastases of gastric cancer origin are indicative of advanced disease, which is rarely amenable to surgery. Despite the overall negative prognosis for patients at this stage of the disease, there are reports in the literature discussing the surgical management of these hepatic metastases and the potential advantage for the patient. The small number of patients makes it difficult to draw any solid conclusions, however the challenge lies in identifying these patients that may actually benefit from surgical management of the metastatic disease. This paper will review the available literature with the goal of identifying criteria, or at least suggestions, as to how to distinguish these patients that should proceed with a surgical resection, as well as discuss the difficulties involved in making any progress in this challenging oncological issue.**

**KEY WORDS:** hepatic metastases, gastric cancer, surgical management, resection criteria

## INTRODUCTION

In the US only, 15% of the 125,000 new cases of colorectal cancer, will have hepatic metastases at the time of diagnosis, whereas another 50% will develop hepatic metastatic disease during the course of the disease.[1] A combination of improved surgical techniques and instrumentation, as well as newer chemotherapeutic agents have led to significantly improved results with the management of hepatic metastases from colorectal cancer and have essentially transformed advanced stage colon cancer to a manageable, if not curable, entity, as there are reports of 30-50% 5 year survival rates.[2-5] The picture is even more encouraging when dealing with hepatic neuroendocrine metastases, with 5 year survival rates of 75%.[6] When the topic changes to noncolorectal, nonneuroendocrine hepatic metastatic disease, then significantly worse outcomes are encountered, whose study is further hindered by the sporadic number of cases.[7-8]

Specifically, in the case of advanced gastric cancer with hepatic involvement by metastatic disease, which can be seen in as many as half of the cases, the expected survival with palliative chemotherapy is not any longer than 6 months approximately.[9] This dismal prognosis has led to

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the conclusion that if there is any possibility of increasing the life expectancy of these patients, then surgery will be the only way to do that. This is further made possible by advances in liver surgery that can help realize such an aggressive strategy. Despite the several small series reporting successful management of these patients, the challenge remain in identifying those patients that will actually truly benefit from this approach. Obviously, the "elephant in the room" when discussing such a topic is the question of tumor biology, which remains unanswered.

In the next few pages, the goal is to review some of the studies dealing with the topic of surgical management of hepatic metastases from gastric cancer, with the aim being to identify the common threads in terms of criteria for a lasting success. Additionally, we will discuss the keys in making such an approach even possible, as well as the challenges remaining in reaching conclusions, and what the future prospects appear to be.

## NOT ALL HEPATIC METASTASES ARE THE SAME!

Surgical management of hepatic metastases of colorectal origin has met with significant success leading to potential cures, something which has not been the case with those originating from other parts of the gastrointestinal tract, including the stomach, even in situations where they may appear resectable.[10-12] There are several suggestions for this finding including the fact that in the case of gastric cancer, hepatic metastatic disease is frequently a sign of more significant and wider spread of the disease, as it is associated more often than not with peritoneal spread or gross lymphatic involvement.[13] Additionally, a possible culprit may be differences in the tumor biology between colorectal and gastric cancer. Specifically, in the case of colorectal cancer, hematogenous spread appears to be less efficient, whereas the preferred site of metastatic spread appears to be primarily the liver, which could be the result of the involvement of specific adhesion molecules. [14-15] Finally, the strategic location of the liver in the venous drainage system of the abdomen in general and the colon specifically, gives it the role of a "trap" for tumor cells in the process of escaping into the systemic circulation. These differences represent an early attempt to explain the significant differences seen regarding the prognosis and success of surgical management of hepatic metastases originating from the colon versus those originating from the stomach. Even so, there remains controlled enthusiasm regarding the surgical management of these gastric metastatic lesions to the liver, given the lack of a better solution and the progress seen in hepatobiliary surgery.

## THE ROLE OF TECHNOLOGY

The prerequisite in discussing the possibility of hepatic resection of metastatic disease is that the ability and the means exist for the procedure to be performed in a safe manner. This has become possible with significant advances in hepatobiliary surgery and anesthesia, including more detailed radiological imaging and navigation systems that allow the mapping of the location of the metastatic lesions and their relation to surrounding vascular and biliary structures. Additionally, there has been progress in the types of instrumentation used for hepatic parenchyma resection, with the ultimate goal being a bloodless resection of the hepatic parenchyma while being able to control vascular and biliary structures. The benefit of the experience that anesthesiologists have accumulated with liver resections and liver transplantation cannot be overstated, as their ability to manage liver physiology and the responses seen during the liver resection are an essential element of controlling blood loss, while preserving function of the hepatic remnant at the same time.

## THE EXISTING EVIDENCE

The main problem is that there is a lack of

organized and sufficient data to draw any firm conclusions regarding the utility of resection of hepatic metastases from gastric cancer. Apart from case reports, there have been few reports with a somewhat significant number of patients. Specifically, a study from Austria included 15 patients undergoing hepatic resection for gastric adenocarcinoma metastases, with an overall median survival of 8.8 months (range 6.1 to 47.3 months) and with two of them surviving longer than three years.[16] Another study from South Korea included 11 patients with hepatic metastatic disease from gastric adenocarcinoma who underwent resection.[17] These patients all had solitary lesions and the median survival of patients with synchronous and metachronous hepatic metastases were 13 and 74.3 months respectively. Yet another study, also from the Far East and specifically Japan, identified 19 patients with primary gastric cancer and synchronous or metachronous hepatic lesions, who underwent surgical resection with the aim of a curative approach.[18] The 1-, 3- and 5-year survival rates after the liver resection were 77%, 34% and 34% respectively, with three of the patients surviving longer than 3 years. In all these studies there is a common thread: no matter how much the different chemotherapeutic regimens for gastric cancer have improved and despite the fact that the result with the surgical approach are not equivalent to those seen in the case of hepatic metastases from colorectal cancer, it is still possible to achieve significant improvement in the survival of many of these patients with the careful application of a surgical strategy.

## HOW DO WE DECIDE?

The question is obviously the one of how to decide which patients will benefit the most from this aggressive approach, so that there can be an improved selection procedure. The first element is that there has to be very accurate staging so that the hepatic lesions are the only metastatic disease identified. Another critical element is the ability to achieve an R0 resection; however, there is a caveat here, as the argument seen in the case of colorectal cancer that the number of metastatic lesions does not matter as long as you can resect all of them, does not seem to hold true in the case of the primary being a gastric cancer, as solitary metastatic lesions seem to be in a better position to lead to extended survival.[17] The paper from Japan had stressed the fact the metastatic lesions were synchronous or metachronous, which is significant, especially in the case of metachronous lesions.[18] In the same paper, the authors add the findings of a fibrous pseudocapsule between the tumor and the surrounding parenchyma, as well as a well-differentiated histologic type. The rationale is that the pseudocapsule could represent the result of an immunomodulatory reaction to the tumor. The importance of the metachronous identification of the metastatic disease was confirmed by another paper, in which the authors also raised the issue of primary tumor location, stating that primary gastric lesion localization within the proximal third of the stomach may be predictive of poor outcome.[16] Finally, in an analysis of 22 patients who had undergone liver resection for metastatic disease from gastric carcinoma from Japan and with overall 1-, 3- and 5-year survivals of 73%, 38% and 38% respectively, also stressed the importance of a solitary lesion, as the best results were obtained with solitary lesions less than 5cm.[19] Overall, the key positive factors appear to be an R0 resection, solitary lesion that is either synchronous or (preferably) metachronous, with the possible addition of a fibrous pseudocapsule.

## REMAINING CHALLENGES

As helpful as these data may be, they still do not provide a complete answer for a variety of reasons. The first one is that we need to explain the differences between the various studies regarding the factors identified. The main reason appears to be the limited number of patients, even in the case of specialized centers, leading to

a type II error. Additionally, even in these centers, most of the reports coming from them group patients with noncolorectal, nonendocrine liver metastatic disease together, which leads to a very heterogeneous group of patients and tumor types. The answer to these problems is conducting multicenter, prospective trials, so that we can move from the empiric to the evidence-based method of making decisions.

The other challenge involved in dealing with these patients with advanced disease is the "X" factor, which is none other than biology of the tumor and our inability to predict how it will affect tumor progression. There is the belief that the worse outcomes seen in the case of liver metastases of gastric origin, compared to those of colorectal origin may be a result of the fact that the hepatic disease may represent only a small part of the generalized spread of the gastric cancer, including seeding of the peritoneum and adjacent organs.[20] The improved results seen in the case of metachronous lesions are essentially an extension of this theory, as they represent a marker of tumor biology, and specifically one showing decreased aggressiveness. Additionally, the difference in the results between the primary being a gastric versus a colorectal cancer, may also have to do with differences in the biological behavior of these two types of cancer. This may also include their drainage patterns, given the more direct venous drainage of the colon to the liver compared to the stomach.

## CONCLUSIONS

This brief review of the issue of surgical management of hepatic metastases of gastric origin has led us to certain conclusions, which are obviously not as solid as we would like given the lack of extensive evidence due to a scarcity of cases. Nevertheless, it can safely be said that surgical management can potentially lead to improved survival, if there is careful patient selection. What constitutes this "careful" selection is also a matter of debate, although there are certain criteria that appear to have more weight than others, such as solitary and metachronous lesions. The biggest challenge remains given that we still need to gain a better understanding of the biology of the primary cancer and the metastatic lesions, in order to have improved patient selection. This probably represents another example where the biggest progress is not going to come from the operating room, but rather from the experimental bench.

## CONFLICT OF INTEREST

The author declares that he has no conflict of interest

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