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OVERVIEW ON GASTRIC CANCER



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Overview on Gastric Cancer

Chapter 1

Gastric neuroendocrine tumors

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1. Introduction

Gastric Neuroendocrine Tumors (NET)s are classified on the basis of criteria that are common to all gastrointestinal and pancreatic neuroendocrine neoplasms. Most neuroendocrine neoplasms of the stomach are NETs –well differentiated, nonfunctioning enterochromaffin-like(ECL) cell carcinoids (ECL cell NETs)-arise predominantly in the corpus-fundus region [1]. Three distinct types are recognized :

1. type I, associated with autoimmune chronic atrophic gastritis (A-CAG) (70-80 percent);
2. type II, associated with multiple endocrine neoplasia type 1 (MEN 1) and Zollinger –Ellison syndrome (ZES) (5 percent)
3. type III , sporadic (i.e not associated with A-CAG or MEN1-ZES) (15-20 percent).

Serotonin producing enterochromaffin (EC) cell , gastrin cell , ghrelin cell or adrenocorticotrophic hormone (ACTH) cell NETs are very rare and may arise in both the corpus-fundus and antrum .

NECs (poorly differentiated endocrine carcinomas), and MANECs (mixed adenoneuroendocrine carcinoma) are also rare and may arise in any part of the stomach [1].

Neuroendocrine Tumor (NET)

NET G1

NET G2

Neuroendocrine Carcinoma (NEC)

Large cell NEC

Small cell NEC

Mixed adenoneuroendocrine carcinoma (MANEC)

EC cell ,serotonin producing NET

Gastrin producing NET(gastrinoma)

Elife s

The classification of neuroendocrine tumors (NET) can help guide diagnosis. In 2010, the World Health Organization (WHO) updated its classification of NETs based on tumor site of origin, clinical syndrome, and differentiation [2,3].

1.2. Site of origin

Gastrointestinal and pancreatic neuroendocrine tumors(GNET) (PNET) are commonly divided by site of origin (eg foregut, midgut, hindgut [2]. Of note, PNETs are considered to originate in the foregut [2]. Distal tumors include NETs in other locations such as ear, heart and ovaries [2].

Foregut: Lungs, stomach,first part of duodenum

Midgut: Second part of duodenum, jejunum, ileum, right colon

Hindgut: Transverse, left sigmoid colon, rectum [2,4,5,6]

NETs also exhibit gender distribution: women are more likely to have a primary NET in the lung,stomach, appendix or cecum; men are more likely to have a primary NET in the thymus, duodenum, pancreas, jejunum/ileum, or rectum [3].

Neuroendocrine neoplasms, which are defined as epithelial neoplasms with predominant neuroendocrine differentiation arise throughout the body. The terminology of neuroendocrine neoplasms arising in the digestive tract has evolved over the past two decades to reflect a separation into two major categories:

Neuroendocrine tumors (NETs), which show a solid, trabecular, gyriform, or glandular pattern with fairly uniform nuclei, salt-and-pepper chromatin, and finely granular cytoplasm.

Neuroendocrine carcinomas, which are high grade carcinomas whose morphology and clinical behaviour resembles small cell carcinoma or large cell neuroendocrine carcinoma of the lung.

Poorly differentiated neuroendocrine carcinomas are often associated with a rapid clinical course, while well-differentiated NETs of the digestive system generally have a much better prognosis. However well-differentiated tumors are not a homogeneous group and a

spectrum of aggressiveness. The biologic behaviour of well-differentiated NETs cannot be predicted based on morphology alone.

1.3. Grade and differentiation

The grade of a tumor refers to its biologic aggressiveness [7]. The grading system is based on the rate of proliferation, which is defined by the number of mitoses per 10 high power microscopic fields or per 2mm² (mitotic rate), or as the percentage of tumor cells that immunolabel positively for the Ki-67 antigen (Ki-67 index) [7]. Briefly, low-grade tumors are characterized by low proliferative indices and are considered indolent in nature [8]. High-grade tumors tend to be poorly differentiated, have high proliferative indices, and are thus very aggressive [8].

NETs can also be classified based on differentiation, which refers to the extent to which cancerous, or neoplastic, cells resemble normal cells [7]. Well-differentiated NETs have a typical organoid arrangement of cells with nesting, trabecular, or gyriform patterns [7]. Well-differentiated NET cells produce large amounts of secretory granules with diffuse immun-expression of neuroendocrine markers [7]. In contrast, poorly differentiated NETs have atypical, sheet-like, diffuse and irregular nuclei, less cytoplasmic secretory granules, and limited biomarker immunexpression [7]. Well-differentiated NETs are usually of low or intermediate grade, poorly differentiated NETs are usually high grade [2-8].

1.4. 2010 WHO classification

The 2010 WHO classification of tumors of the gastrointestinal tract, liver, and pancreas also endorsed the ENETS (European Neuroendocrine Tumor Society) grading scheme for neuroendocrine neoplasms of the digestive tract. Separating well-differentiated tumors into low-grade (G1) and intermediate grade (G2) categories [8,9]. All poorly differentiated neuroendocrine tumors are high grade (G3) neuroendocrine carcinomas according to this classification scheme.

The best cutoff to separate low-grade (G1) from intermediate grade (G2) tumors is not established. The 2010 WHO classification uses 2 mitoses per 10 HPF, and/or <3 percent Ki-67 staining as the cutoff values [10,11] (Table 1).

Several studies have challenged the assumption that poorly differentiated histology and high tumor grade are equivalent. There is a small subset of patients with neuroendocrine tumors that appear histologically well differentiated with less than 20 mitoses/10 high power fields (HPF, G2 by mitotic count) but are associated with high Ki-67 proliferation indices (>20 percent) that fall into the high-grade (G3) range in the current WHO grading scheme. The clinical behaviour of these grade concordant tumors is somewhat worse than grade-concordant

well-differentiated G2 tumors, but better than that of bona fide poorly differentiated NECs [12].

These data support the view that the current WHO G3 category is in fact heterogeneous, containing two distinct groups of neoplasms, and can be further separated into well-differentiated NET with an elevated proliferation rate (WD-NET,G3) and poorly differentiated NEC. Furthermore, the presence of a cohort of neoplasms with a lower Ki-67 index (20 to 55 percent) within the cohort of high grade neuroendocrine carcinomas, which respond less well to platinum-based chemotherapy but survive longer than those with Ki-67 >55 percent, adds further support to the heterogeneity of the current G3 category [13].

1.5. Assessment of Ki-67 labeling index

The optimal cutoff value for the Ki-67 labeling index to distinguish low, intermediate, and high grade gastroenteropancreatic NETs has not been conclusively established. However, the ENETS, American Joint Committee of Cancer (AJCC) and the 2010 WHO classification include a uniform Ki-67 labeling cutoff <3 percent to define low-grade (G1), 3 to 20 percent for intermediate grade (G2), and >20 percent for high-grade NETs [10,11].

The Ki-67 protein is a large nuclear protein (395 kDa) that is closely associated with the nucleolus and heterochromatin. Ki-67 is expressed in G1, S, G2, and M phase, with a peak level during mitosis. The exact function of Ki-67 is unknown, but it appears to be involved in cell cycle regulation and/or organization of the nucleolus; removal of Ki-67 prevents cell proliferation [14,15]. More recent studies have utilized the monoclonal MIB-1 antibody, which works well on formalin-fixed, paraffin-embedded tissue.

The use of a 3 percent cutoff point to stratify prognosis among well-differentiated pancreatic NETs is supported by subsequent studies [16,17], and most groups, including the ENETS and WHO, use a uniform cutoff of <3 percent to define low-grade (G1) from intermediate grade NETs of the digestive tract [10,11].

Through the mid 2000s, the proliferative rate that was used to define poorly-differentiated (high grade) neuroendocrine carcinomas (NECs) was 10 percent, and this was the rate used in the 2004 WHO classification and in several studies [18]. In 2006, and 2007, the ENETS proposed to raise this rate to 20 percent, which was endorsed by the WHO and AJCC [10,11]. However, at least some data suggest that this cutoff point may require further modification. A clinical study of WHO G3 gastrointestinal NECs found that patients with Ki-67 <55 percent had a lower response rate to platinum-based chemotherapy (15 versus 42 percent, $p < 0.001$), but better survival (14 versus 10 months, $p < 0.001$) than did those patients with Ki-67 ≥ 55 percent [13].

1.6. Other parameters and markers for histologic grading

Lymphovascular and perineural invasion are not part of the grading criteria, although they should be recorded as a prognostic factor. Historically, immunohistochemical staining for PCNA (proliferating cell nuclear antigen) was considered an alternative marker of proliferative activity; however, it fell out of favor due to a lack of reliability [19].

Several other newer markers have been reported to have prognostic value in NETs. CK 19 (cytokeratin -19) is a marker of pancreatic ductal epithelium but also transiently expressed in islet cells. Its expression has been shown to correlate with worse survival in pancreatic NETs [20]. A classification scheme based upon expression of CK 19 and CD 117 (KIT) has been proposed, with CK 19+ CD 117+ pancreatic NETs having the shortest survival [21]. Those markers may be useful in primary NETs, but they appear to have any prognostic significance in metastatic disease, unlike the Ki-67 labeling index [17].

Table 1: Histopathology of Neuroendocrine Tumors [8]

Histological Classification	Well differentiated (Low grade ,G1)	Moderately Differentiated (Intermediate Grade,G2)	Poorly Differentiated (High Grade, G3)
Appearance	Monomorphic population of small, round cells	*	Cellular pleomorphism
Prognosis	Prolonged survival	Intermediate	Poor
Mitotic rate	<2	2-20	>20
Ki-67 index *	<3%	%3-20	>20%
Necrosis	Absent		Present

*Not well defined in medical literature.

Ki-67 index applies only to WHO and European Neuroendocrine Tumor Society (ENETS) classification of gastroenteropancreatic NET.

2. Clinical syndrome

NET can also be classified as functional or nonfunctional [4]. NETs are considered functional when a specific clinical syndrome is induced due to the excessive production of hormones by the tumor cells; approximately two-thirds of NETs are functional [2]. Examples of functional NETs include carcinoid tumors, which can result in carcinoid syndrome, and functional pancreatic NET (insulinomas, gastrinomas, vasoactive intestinal peptide (VIP)omas, glucagonomas and somatostatinomas [4].

Nonfunctional NETs are not associated with a clinical syndrome, but can still produce symptoms related to the presence of the tumor or its metastases (eg abdominal pain and bloating) [7,22]. Functional and nonfunctional PNET may be benign or malignant [4].

2.1. Staging system

The WHO also endorsed staging neuroendocrine neoplasms using the specified TNM-based system. The most recent 7th edition of the AJCC staging manual, which reflects a modification of proposal by ENETS [10], includes separate TNM staging systems for NETs of the appendix, pancreas, stomach (table 2), small bowel/ampulla of Vater, and colorectal primary sites .

2.2. TNM staging of gastric net

Table 2: American Joint Committee on Cancer Staging for NET of the Stomach (AJCC Cancer Staging Manual, seventh edition /2010, published by Springer, New York ,Inc.) [23].

Stage 0	Tis	Stomach	Carcinoma in situ/ dysplasia(tumor size less than 0.5 mm),confined to mucosa	N0 No regional lymph node metastases	M0 No distant metastases
Stage I	T1	Stomach	Tumor invades lamina propria or submucosa and size 1 cm or less	N0 No regional lymph node metastases	M0 No distant metastases
Stage IIA	T2	Stomach	Tumor invades muscularis propria or size greater than 1 cm	N0 No regional lymph node metastases	M0 No distant metastases
Stage IIB	T3	Stomach	Tumor penetrates subserosa	N0 No regional lymph node metastases	M0 No distant metastases
Stage III A	T4	Stomach	Tumor invades visceral peritoneum(serosal) or other organs or adjacent organs or adjacent structures	N0 No regional lymph node metastases	M0 No distant metastases
Stage IIIB	Any T			N1 Regional lymph node metastases	
Stage IV	Any T	Stomach		Any N	M1

3. Clinical guidelines for the treatment of gastric neuroendocrine tumors

The following organizations have issued clinical guidelines for the treatment of carcinoid tumors:

National Comprehensive Cancer Network (NCCN)

North American Neuroendocrine Tumor Society (NANETS)

European Neuroendocrine Tumor Society (ENETS)

European Society for medical Oncology (ESMO)
UK and Ireland Neuroendocrine Tumor Society (UKI NETS) [24].

3.1. Treatment for locoregional disease

NCCN guidelines recommend resection as the primary treatment for most carcinoid tumors of the gastrointestinal (GI) tract, lung and thymus. Specific recommendations vary by tumor subtype. However, for neuroendocrine tumors at any site, cholecystectomy is recommended during surgical resection if treatment with a somatostatin analog (i.e, octreotide, lanreotide) is planned, due to the increased rate of biliary problems associated with long-term use of these agents [24].

For gastric tumors, the NCCN recommendations are as follows [24]:

*With hypergastrinemia and tumors ≤ 2 cm: Endoscopic resection with biopsy or observation; or octreotide or lanreotide for patients with Zollinger –Ellison syndrome .

*With hypergastrinemia and tumors >2 cm: Endoscopic resection and regional lymphadenectomy; endoscopic resection, if possible, or surgical resection

*With normal gastrin levels: Radical gastric resection and regional lymphadenectomy: endoscopic or wedge resection can be considered for tumors ≤ 2 cm .

In 2013, NANETS released updated guidelines with the following recommendations for treatment of gastric carcinoid tumors [25]:

- Type I or II, <1 cm: Surveillance or endoscopic removal
- Type I, 1cm to <2 cm: Surveillance with repeat endoscopy every 3 years or endoscopic resection
- Type II, 1cm to <2 cm: Endoscopic resection
- Type I, ≥ 2 cm (≤ 6 polyps), or type II ≥ 2 cm: Endoscopic resection, if possible , or open surgical resection
- Type I, ≥ 2 cm (>6 polyps): Individualized treatment required; surveillance, endoscopic resection, or surgical resection.
- Type III: Partial gastrectomy and lymph node dissection

The 2016 revised ENETS guidelines prefer conservative management strategies over surgery for type I tumors. The guidelines recommend resection of tumors ≥ 10 mm performed by endoscopists experienced in gastric tumor, using either endoscopic mucosal resec-

tion (EMR) or endoscopic submucosal dissection(ESD) [26].

For type II tumors, limited excision can be recommended, but this should be patient tailored at multidisciplinary NET centers of excellence. Type III tumors should be treated similarly to gastric adenocarcinoma with surgery (partial or total gastrectomy with lymph node dissection). Systemic therapy is required for inoperable or stage 4 disease [26].

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Overview on Gastric Cancer

Chapter 2

Defining appropriate field arrangements for the adjuvant postoperative therapy of gastric cancer

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1. Introduction

The optimization of the treatment plans provided by the conformational radiotherapy should improve the coverage of the target volume, the dose distribution with respect to the defined critical organs (liver, kidneys, intestine, duodenum). A four or five-beam technique appears to decrease toxicity and should be preferred in practice.

2. Three dimensional conformal radiation therapy

2.1. Ballistics

At the Mayo Clinic, a retrospective review of 63 patients treated with postoperative radiotherapy with or without chemotherapy, suggested improved toxicity outcomes associated with use of four or more radiation fields [1]. In this series, 22% of patients treated with AP-PA techniques developed grade 4 or 5 complications vs. 4% of patients treated with 4 or more fields. Soyfer et al implemented a non-coplanar 3-dimensional conformal RT (3D CRT) technique that used four fields, including right and left laterals, an anterior cranio-caudal oblique field, and an anterior caudal-cranial oblique field [2]. A total of 19 patients each underwent planning using three techniques: non-coplanar 3D CRT, AP-PA, and four-field box. The 3D CRT technique resulted in equivalent clinical target volume coverage with significantly decreased dose to the kidneys and spinal cord. The use of multi-beam techniques significantly reduces toxicity[3]. Twenty-two percent of patients had grade 4 toxicity if a two-beam technique was used compared with 4% for a technique with at least four beams ($p = 0.045$) according to

EORTC-RTOG expert opinion [3]. The optimization of the treatment plans provided by the conformational radiotherapy should also improve the coverage of the target volume, the dose distribution with respect to the defined critical organs (liver, kidneys, intestine, duodenum). A four- or five-beam technique appears to decrease toxicity by improving the conformation factor (percentage of the target target volume receiving a dose ≥ 45 Gy), protection of healthy tissues (ratio of healthy tissue volume receiving a dose ≥ 45 Gy on the volume of the isodose 45 Gy) [4]. A split-field mono-isocentric conformal technique using six radiation field, was developed at the Peter MacCallum Cancer Centre in Australia [5]. This technique divides the planning target volume (PTV) into two abutting sections, the upper half including the tumor bed, anastomosis, and splenic hilar nodes and the lower half including the subpyloric, pancreaticoduodenal, and paraaortic nodes. The upper half is treated with an anterior field, a posterior field, and a left lateral field that is angled as necessary to avoid the spinal cord. The lower half is treated with a right lateral, left lateral, and anterior field that are angled to minimize kidney dose. A total of 15 patients were each planned using the split-field conformal technique and a standard AP-PA arrangement. Dose-volume histogram comparisons revealed improved PTV coverage and lower RT doses to the kidneys and spinal cord using the split-field conformal technique [5,6]. A four- or five-beam ballistic standardization has been proposed [7]. A technique with four orthogonal beams can be used, or better, a five-beam technique with some variability inciting to propose two types of standardized balistics [7] (Table 1).

Table 1: Balistics with 4 or 5 beams after optimization in gastric cancer treatments in the postoperative situation. Two groups of patients possible. Group 2 accounts for 75 % of the situations and group 1: 25 % [7].

Obliquity	Beam 1	Beam2	Beam3	Beam4	Beam5
Cardia:					
Group 1	180°	135°	93°	42°	338°
Group 2	180°	90°	45°	349°	329°
Gastric Fundus					
Group 1	180°	90°	44°	0°	325°
Group 2	181°± 5°	135°±2°	93°±4°	43°± 12°	333°±7
Antrum					
Group 1	181°±5°	134°±-1.6°	93°±4.8°	43°±12°	335°±4°
Group 2	180°	94°±9°	47° ±8°	353°±11°	307°±26°

2.2. Dosimetry

A three-dimensional treatment plan is realized with correction of the inhomogeneities. The treatment plan should respect the recommendations of the International Commission on Radiation Units and Measurements (ICRU Reports 50 and 62). The dose-volume histograms of each volume are made. Ninety-five percent of the target volume receives more than 95% of the prescribed dose. Inhomogeneities of dose will be accepted with an interval between +7%

of prescribed dose and -5% (calculation volume less than 1.8 cm) [4].

2.3. Organs at risk and dose constraints

The lungs, kidneys, liver, heart and spinal cord are delineated and defined as an organ at risk. Recommendations were made, including those from the European Organization for Research and Treatment of Cancer (EORTC) group in a preoperative situation [3]. The maximum dose to the marrow should not exceed 45 Gy. The percentage of total pulmonary volume receiving 20 Gy or more (V20) is ideally 30% or less. The liver also represents a critical organ. The liver volume receiving 30 Gy or more (V30) is less than 30%; The average dose to the liver is less than 21 Gy. If lateral beams are used, they provide a limited dose of 20 Gy [4].

3. Intensity-modulated radiation therapy

Several recent reports have examined intensity modulated radiation therapy (IMRT) for the delivery of postoperative radiation. In order to assess the potential advantages of IMRT for the delivery of adjuvant radiation, dosimetric comparison were made in five series [8,9]. The IMRT plans, compared to conventional 3D planning, reduced dose to the kidney [8,9]. Although most series of IMRT have been limited to dosimetric plan comparisons, one small series described outcomes among 7 patients treated with IMRT. The IMRT plans provided excellent target coverage and significantly reduced liver and kidney doses when compared with anterior-posterior and three-field plans. No patient experienced greater than grade 2 acute gastrointestinal toxicity. A number of limitations of IMRT were identified. There is a need for detailed information regarding organ motion in the upper abdomen and implementation of breath hold or gating techniques may be necessary prior to adoption of IMRT in routine clinical practice [9].

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Overview on Gastric Cancer

Chapter 3

The Principles of the Surgical Management of Gastric Cancer

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Abstract

Surgery is the only curative therapy for gastric cancer but most operable gastric cancer presents in a locally advanced stage characterized by tumour infiltration of the serosa or the presence of regional lymph node metastases. Surgery alone is no longer the standard treatment for locally advanced gastric cancer as the prognosis is markedly improved by perioperative chemotherapy. The decisive factor for optimum treatment is the multidisciplinary team (MDT) specialized in gastric cancer. However, despite multimodal therapy and adequate surgery only 30% of gastric cancer patients are alive at 3 years. This article reviewed the principles of the surgical management of gastric cancer (minimally-invasive or open) and how this may optimize multimodal treatment.

Keywords: gastric cancer; surgery; multimodal treatment

Abbreviations: EMR: endoscopic mucosal resection; ESD: Endoscopic submucosal dissection; ECF: epirubicin, cisplatin and infusional fluorouracil; ECX: epirubicin, cisplatin and capecitabine; OTG: open total gastrectomy; LATG: laparoscopy-assisted total gastrectomy; BMI: Body mass index; AUGIS: association of upper gastrointestinal surgeons; BSG: British Society of gastroenterology; BASO: British Association of surgical oncologists

1. Introduction

Gastric adenocarcinoma are divisible into two subtypes which are distinct in their natural history and aetiology. The subtype that remains endemic in Far East, parts of S America and Eastern Europe is principally a disease of the distal stomach associated with chronic gastritis, intestinal metaplasia and atrophy of mucosa. The high incidence rates in these regions is thought to be due to continuing high rate of *H. pylori* infection, adverse dietary factors (nitrosamines) and genetic predisposition [1]. The increasingly occurring subtype found in Western countries is commonly found near the GOJ and is associated with significant gastritis [2]. Associated with the marked increase in incidence of GOJ cancer over the last 30 years is

the downward migration of oesophageal tumours and proximal shift of gastric tumours. GOJ cancer is the fastest increasing solid malignancy of adult life in the West with an increasing incidence of 3-4% per annum [2]. Siewert and Stein proposed a classification system of GOJ cancers in an attempt to simplify the conundrum. (**Table 1**) [3]. However, only specialist oesophagogastric surgical centres can accurately classify the tumour of GOJ as arising in distal oesophagus, gastric cardia or subcardinal stomach [4]. Being a loco-regional disease, the primary objective of surgery is to excise the primary tumour with clear longitudinal and circumferential resection margin, with combined organ resection as required (R0 resection) and resection of associated lymph nodes; then safely restoring intestinal and biliary continuity to allow adequate nutritional intake [5,6].

2. Patient Pathway and Selection for Gastric Surgery

Only 40% of early gastric cancer are associated with symptoms and 80% of gastric cancer patients present with > T1 disease. 65% patients present as advanced cancers (T3,T4), 85% have lymph node metastases and 40% are metastatic (**Table 2**) [4,7]. 25% will require endoscopic, radiological or surgical procedures for haemorrhage, obstruction, pain or perforation [2]. Physical signs develop late and most commonly associated with locally advanced or metastatic disease. Evidence from studies of early gastric cancers from Japan suggest that well-differentiated cancers may metastasize more frequently to the liver and poorly-differentiated tumours to lymph nodes [5]. This may explain the high rate of local recurrence with the poorly-differentiated tumours. In all cases microscopic proof of malignancy is required. Once staging investigations are complete, the patient is discussed at the specialized MDT, to propose an individually tailored management plan [6]. The final pathological stage, following curative surgery assists in determining prognosis. Survival is significantly poorer among patients with final pathological stages II,IIIa and IV (**Tables 3,4**) [8].

3. Types of gastrectomy and extent of lymphadenectomy

3.1. Historical controversies

During the 1970's, enthusiasts in West suggested the concept of total gastrectomy as appropriate radical surgical management of gastric cancer- '*total gastrectomy 'de principe'*'. They argued there was less risk of positive proximal resection margin, that gastric cancer is multicentric disease, with gastric mucosal field change, and with subtotal gastrectomy there was inadequate lymphadenectomy (missed left cardia group). In Japan, however, total gastrectomy was only carried out (*total gastrectomy 'de necessitate'*) when required to allow R0 resection to be achieved, whilst subtotal gastrectomy was carried out for many antral tumours with satisfactory results. The pattern of lymphatic spread in antral cancers should indicate that removal of left cardiac, short gastric, splenic hilum, and distal splenic artery nodes are unlikely to improve outcome (5% involved and, if positive, poor prognostic sign). The issue of positive

margins is mainly due to inaccurate diagnosis of proximal extent of tumours [5,6]. Several RCTs were carried out which showed no difference in post-operative morbidity or mortality, or difference in 5-year survival. Indeed, some showed that 5-year survival after subtotal was better than after total gastrectomy. Total gastrectomy has greater long-term HRQL deficit than subtotal surgery [11].

3.2 Western radical: (AUGIS/BSG/ BASO) guidelines 2011

The type of gastrectomy depends on the site of the primary tumour with the resection margin aimed at a 5cm minimum from the palpable edge of the tumour. Total gastrectomy is for the ‘diffuse’ (according to the Lauren classification) type tumours which are more prone to lateral spread [5,6,14]. Total gastrectomy may not be necessary for distal tumours as long as adequate staging, mapping biopsies, careful radiological review, on-table oesophagogastroduodenoscopy (OGD) with or without frozen section are satisfactory [5,15]. Distal third cancers (tumours of the gastric antrum) will require a subtotal (80%) gastrectomy, including division of the left gastric artery and vein, and excision of regional lymphatic tissue [6]. Total gastrectomy is performed only when there is a large distal third tumour or when submucosal tumour infiltration is within 7-8cm of GOJ [5]. Limited gastric resections is suggested only for palliation or in the very elderly [15]. Distal pancreas and spleen is not to be resected for a cancer in the distal two-third of stomach as there is no oncological advantage but increased morbidity [15]. The middle third cancers (tumours of the gastric body) often requires total gastrectomy as it depends on the proximal margin of the tumour. The amount of stomach remaining below GOJ should be a minimum of 2cm. Serosa negative cancer requires 7cm margin from GOJ and serosa positive cancer requires 8cm from GOJ. Smaller margins are acceptable in elderly patients especially if ‘intestinal type’ (according to the Lauren classification) [14,15]. Proximal third cancers are tumours of the gastric cardia. Siewert 3 GOJ tumours may be amenable to total gastrectomy if enough proximal clearance is possible. True junctional tumours (Siewert 2) is treated with extended total gastrectomy or cardio-oesophagectomy [10]. All patients with proximal gastric tumours, should be made aware that at time of dissection/resection, it may be necessary to proceed to caedio-oesophagectomy with possible thoracotomy, so as not to compromise resection margins. The overall aim of surgery is adequate local clearance, appropriate lymphadenectomy (formal D2 and posterior mediastinal, perioesophageal nodes) and an uncomplicated anastomosis with low morbidity [5,6,15]. Ex vivo proximal margin of > 3.8cm of normal oesophagus (5cm *in vivo*) is associated with minimal risk of anastomotic recurrence and an independent predictor of survival. Intraoperative frozen section is standard. Splenic and hilar node resection should only be considered in patients with tumours of proximal stomach located on greater curvature/ posterior wall of stomach close to splenic hilum where incidence of splenic hilar nodal involvement is likely to be high [5,13,15]. There is marked health-related quality of life (HRQL) deterioration after gastrectomy, and total gastrectomy has greater

long-term HRQL deficit than sub-total surgery [16,17]. However, 95% near total gastrectomy which includes complete resection of the gastric fundus and complete cardial lymphadenectomy (groups 1 & 2) with a little (2cm) gastric pouch has similar oncological outcome but offer best short-term results such as lower anastomotic leak rate and a better quality of life than total gastrectomy. This is because of the limited disruption of the oesophago-gastric junction [18]. In addition, the anastomosis of the distal stomach to the oesophagus following a proximal subtotal gastrectomy may produce a poor functional result because of alkaline reflux that can be very troublesome and difficult to control.

3.3. D1 versus D2 lymphadenectomy

D1 lymphadenectomy is when all N1 nodes (peri-gastric nodes closest to primary) removed en bloc with the stomach (limited) and D2 is when all N1 and N2 (distant peri-gastric nodes and nodes along main arteries supplying stomach) are systematically removed en bloc with stomach. The observation that gastric cancer commonly remained localized to stomach and adjacent lymph node corroborates the Japanese view that radical systemic D2 lymphadenectomy has an increased survival benefit [19]. Excision of the primary lesion with omentum, and N1 and N2 lymph nodes can cure patients even in presence of lymph node metastasis [15,16]. Originally, to ensure full nodal clearance along the splenic artery a routine en bloc resection of spleen and distal pancreas was performed. The Western non-radical view is that more radical lymphadenectomy only gives more accurate pathological staging, rather than confer improved survival benefit. The MRC D1 vs D2 lymphadenectomy trial concluded in 1999 that the classical Japanese D2 had no survival benefit over D1. However D2 resection without pancreaticosplenectomy may be better than standard D1 [6,16]. The Dutch D1D2 trial 15-year results of 2010 demonstrated an overall survival in 15 years of 21% D1 and 29% D2 group. The gastric cancer-related death rate was significantly higher in the D1 group 48% vs D2 group 37%. Local recurrence of 22% D1 group vs 12% D2. Operative mortality of D2 was significantly higher 10 vs 4%, and complication rate 43% vs 25%, D2 vs D1. 20% of D2 group with N2 nodes were still alive at 11 years; unlikely if D1 alone was performed [15]. Overall D2 has lower locoregional recurrence and gastric cancer-related death rates. It has significantly higher post-operative mortality, morbidity and reoperation rates. Spleen-preserving D2-resection is thus recommended for resectable gastric cancer [16,20]. The current European description of D2 lymphadenectomy involves removal of >15 lymph nodes, irrespective of node stations [5,6]. Extended D3 lymphadenectomy is a more radical en bloc resection including N3 nodes outside normal lymphatic pathways from stomach, involved in advanced stages e.g. station 12 (hepatoduodenal ligament) or by retrograde lymphatic flow due to blockage of normal pathways. Station 12 nodes are involved in 9% of lower third and 4% of middle third cancers. Five-year survival rates of up to 25% have been reported in Japan for patients who have had positive station 12 nodes resected. This manoeuvre is probably worth while in

distal cancers where N2 nodes appear involved. There is no advantage of D3 vs D2, but D3 vs D1 showed improved overall survival [21-23]. Uptake of radical resection remains poor in the West due to relative technical difficulty of achieving nodal clearance, more GOJ tumours, adiposity and lack of formalized training in systematic lymphadenectomy. Practice is likely to change as training is increasingly centralized at high volume centres with lower operative mortality and lower failure to rescue rates due to astute management of complications [11,24]. The future trend is towards lymphadenectomy being tailored to individual preoperative and operative staging, age and fitness [6,16,19]. For early gastric cancer not suitable for endoscopic resection, proximal or distal partial resection with limited lymphadenectomy (N1 tier LN plus station 7 and 8a (D1a)) for mucosal disease and coeliac axis nodes (station 9) (D1b for submucosal disease is recommended. Japanese experience has also confirmed that it achieved the same outcome as standardised D2 lymphadenectomy).

4. Strategies to Minimize Loco-Regional Recurrence

A rational approach to surgery for gastric cancer requires an understanding of the modes of spread of this cancer and how it recurs after surgery. This knowledge is essential in defining the aims and limitations of radical surgery. Gastric cancer is a loco-regional disease with 80% recurrence rates in patients with T4 serosal positive disease. Thus radical surgery in T4 disease produces little benefit [13]. The majority of recurrences occur locally either in gastric bed, retroperitoneum or anastomosis, rather than distant metastases [25]. The median time to recurrence is 2 years. T1/T2 serosal negative disease as expected show fewer recurrences, but those that recur does so later. Distant liver failure (liver metastases) is potentially due to the aggressive sub-set that micrometastasizes early [13]. Strategies to prevent gastric bed recurrence include a meticulous surgical technique with en-bloc resection of stomach, affected adjacent organs and intact gastric lymphatic chains to prevent iatrogenic cell spillage and prevent peritoneal dissemination [16]. Two successful strategies are available to improve outcomes in patients with localized gastric cancer [6,26]. The results of a large North American study (Gastrointestinal Cancer Intergroup Trial INT 0116) reported that postoperative chemoradiotherapy conferred a survival advantage compared with surgery alone, which led to the regimen being adopted as a standard of care [27]. More recently the MAGIC/UK Medical Research Council (MRC) trial demonstrated that perioperative chemotherapy resulted in an improvement in overall survival and progression free survival. Peri-operative chemotherapy is the standard of care in UK and most of Europe for localized gastric cancer with the accepted regimens of ECF or ECX [16,28]. The MRC MAGIC trial have recommended neoadjuvant/ adjuvant chemotherapy in conjunction with adequate surgery (multimodal therapy) to improve outcomes in gastric cancer. Three cycles ECF chemotherapy before and three cycles after surgery were compared to surgery alone. Peri-operative chemotherapy showed an increased 5-year survival rate from 23 to 36% [28,29]. Similar results were achieved in the French study of periopera-

tive cisplatin and FU [30,31]. Adjuvant chemotherapy alone may confer a survival benefit and should be considered in patients at high risk of recurrence who have not received neo-adjuvant therapy (Japanese ACTS-GC trial) [32,33]. However, despite multimodal therapy and adequate surgery only 30% of gastric cancer patients are alive at 3 years [16,28]. As approximately 15% of gastric and oesophagealjunctional adenocarcinoma over express human epidermal growth factor receptor- 2 (HER2) on the cell membrane HER2 a tyrosine kinase receptor can be targeted by monoclonal antibody bevacizumab. The MRC ST03 trial compared ECX and bevacizumab with ECX alone for cancer of the stomach, oesophagus, or junction of stomach and oesophagus (stage 1b (T1N1) II,III or stage IV (T4,N1 or N₂MO), Type III GOJ adenocarcinoma). Chemotherapy in three cycles over 9weeks, 5-6 weeks break then surgery. The safety was marred by perforations at primary tumour, cardiac toxicity, wound healing complications and GI bleeding [34,35]. Trials are underway to assess the usefulness of this regime. Recent randomized trials from China revealed a survival benefit with preoperative radiotherapy (30 vs 20%) [36]. Currently trials are under way in the west to try and replicate this. Post-operative chemoradiation is the standard of care in the USA and for all patients with positive resection margins. With longer-term (>11years) follow-up, the benefits of both the overall survival (35 vs 27 months) and disease-free survival (DFS) (27 vs 19 months) were maintained [6]. There is less enthusiasm in the UK and in Europe because of the toxicity of abdominal chemoradiotherapy such as nausea and vomiting, myelosuppression including neutropenia, fatigue, mucositis and diarrhoea. In addition, the benefit is uncertain post ‘optimum’ surgery. It may, however, be considered in patients at high risk of recurrence i.e. no neoadjuvant therapy and/or suboptimal surgery, e.g. in emergency context and in selected patients after an R0 resection [16].

5. Laparoscopic versus opengastrectomy

5.1. Principles

The same principles that govern open surgery is applied to laparoscopic surgery. In order to ensure the same effectiveness of LG as conventional open gastrectomy, all the basic principles such as properly selected patients, sufficient surgical margins, standardized D2 lymphadenectomy, no-touch technique etc, should be followed [34-38]. As laparoscopic experience has accumulated, the indications for laparoscopic gastrectomy (LG) have been broadened to patients with advanced gastric cancer.

5.2. Indications

Laparoscopic gastrectomy may be considered as a safe procedure with better short-term and comparable long-term oncological results. compared to open gastrectomy [32]. In addition, there is HRQL advantages to minimal access surgery [12]. There is a general agreement that a laparoscopic approach to the treatment of gastric cancer should be chosen only by sur-

geons already highly skilled in gastric surgery and other advanced laparoscopic interventions. Furthermore, the first procedures should be carried out during a tutoring program. Diagnostic laparoscopy is strongly recommended as the first step of laparoscopic as well as open gastrectomies [33]. The advantage of early recovery because of reduced surgical trauma would allow earlier commencement of adjuvant chemotherapy and the decreased hospital stay and early return to work may offset the financial costs of laparoscopic surgery. The first description of LG was given by Kitano, Korea in 1994 and was initially indicated only for early gastric cancer patients with a low risk lymph node metastasis [34,35]. As laparoscopic experience has accumulated, the indications for laparoscopic gastrectomy (LG) have been broadened to patients with advanced gastric cancer. However, the role of LG remains controversial, because studies of the long-term outcomes of LG are insufficient [35]. The Japanese Gastric cancer Association guidelines in 2004 suggested EMR or ESD for stage 1a (cT1N0M0) diagnosis; Patients with stage 1b (cT1N1M0) and cT2N0M0) were referred for LG [36]. Totally laparoscopic D2 radical distal gastrectomy using Billroth II anastomosis with laparoscopic linear staplers for early gastric cancer is considered to be safe and feasible. LTG shows better short term outcomes compared with OTG in eligible patients with gastric cancer. There was significant reduction of intraoperative blood loss, a reduced risk of post-operative complications and shorter hospital stay [37]. Western patients are relatively obese and there is an increased risk of bleeding if lymphadenectomy is performed. LG is technically difficult in the obese than in the normal weight due to reduced visibility, difficulty retracting tissues, dissection plane hindered by adipose tissue, and difficulty with anastomosis. Open gastrectomy is thus preferable for the obese [38]. Obesity is not a risk factor for survival of patients but it is independently predictive of post-operative complications. Careful approach is being needed, especially for male patients with high BMI [6,11].

5.3. Robotic surgery

Robotic surgery will become additional options in minimally invasive surgery. The importance of performing effective extended lymph node dissection may provide the advantage of using robotic systems. Such developments will improve the quality of life of patients following gastric cancer surgery. However, a multicenter study with a large number of patients is needed to compare the safety, efficacy, value (cost/efficacy ratio) as well as the long-term outcomes of robotic surgery, traditional laparoscopy and the open approach [34,39].

6. Conclusions

Gastric cancer is a locoregional disease and adequate surgery is for locoregional control which is mostly ‘treatment’ only. ‘Cure’ requires neoadjuvant/adjuvant chemotherapy to attack the putative micrometastases and prevent local recurrence. Perioperative chemotherapy is currently standard treatment for resectable gastric cancers but neoadjuvant and adjuvant therapies

are no substitute for inadequate surgery. Minimally-invasive surgery has the advantage over open gastrectomy in reducing surgical trauma, improved nutrition, reduced post-operative pain, rapid return of gastrointestinal function, shorter hospital stays with no reduction in curability. The optimization of multimodal therapy is by ensuring adequate surgery for an individual patient. This is based on the decision of the specialist oesophagogastric multidisciplinary team (MDT) following the staging and assessment of fitness for treatment or palliation

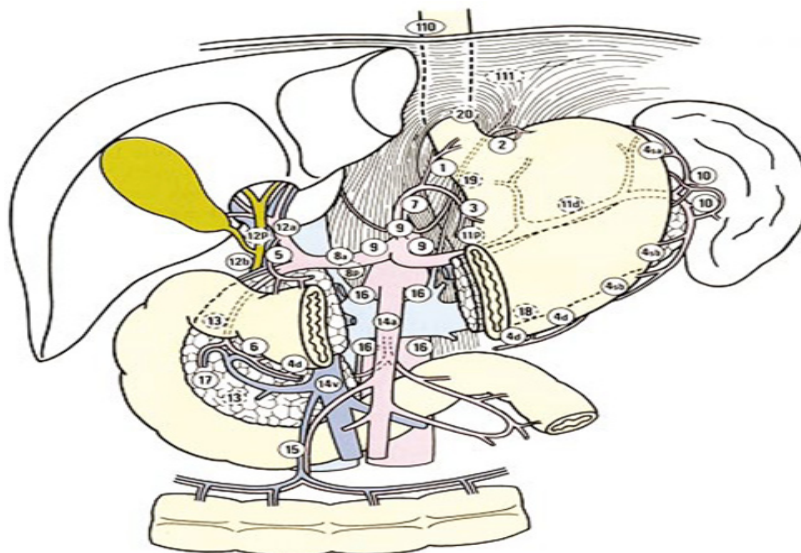


Figure 1: The lymph node stations according to the Japanese classification.

Table 1: Siewert’s classification of GOJ adenocarcinomas [3] (with permission from Siewert JR, Feith M., Werner M., Stein H.J. Ann. Surg. 2000; 232(3): 353-3(61)).

Type 1	Adenocarcinoma of distal oesophagus arising in Barrett’s segment, which may infiltrate GOJ from above
Type 2	True junctional carcinoma of the cardia
Type 3	Subcardinal carcinoma, which may infiltrate GOJ from below

Table 2: TNM 7 classification of gastric cancer [6]. (With permission from: The TNM Classification of malignant tumours 7th edn; eds Leslie H Sabin, Mary K. Gospodarowicz, Christian Wittekind, copyright 2009 with permission of Wiley- Blackwell.)

T	N	M
T1: invades lamina propria or submucosa	N0 : no involved regional lymph nodes	M0: no distant metastases
T1a- invades lamina propria or muscularismucosa		
T1b- invades submucosa		
T2: invades muscularispropria	N1: 1-2 regional lymph nodes involved	M1: distant metastases
T3: invades sub serosa	N2: 3-6 regional lymph nodes involved	
T4: invadesserosa	N3a: 7-15 lymph nodes involved	
T4a-perforate serosa		
T4b- invades adjacent structures	N3b: >15 regional lymph nodes involved	

Table 3: TNM 7 staging of gastric cancer [6]

Stage 0	Tis, N0, M0		
Stage 1A	T1, N0, M0	Stage IIIA	T4a, N1, M0
Stage 1B	T1, N1, M0 T2, N0, M0		T3, N2, M0 T2, N3, M0
Stage IIA	T3, N0, M1 T2, N1, M0 T1, N2, M0.	Stage IIIB	T4b, N0, N1, M0 T4a, N2, M0 T3, N3, M0
Stage IIB	T4a, N0, M0 T3, N2, M0 T2, N3, M0	Stage 111C	T4a, N3, M0 T4b, N2, N3, M0
		Stage IV	Any T, Any N, M1

Table 4: 5-year survival rates [6]. (With permission from: The TNM Classification of malignant tumours 7thedn; eds Leslie H Sabin, Mary K. Gospodarowicz, Christian Wittekind, copyright 2009 with permission of Wiley- Blackwell.)

Stage 0	>90%
Stage 1A	60-80%
Stage 1B	50-60%
Stage 11	30-40%
Stage 111B	20%
Stage 111C	10%
Stage 1V	< 5%

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Overview on Gastric Cancer

Chapter 4

HER-2: A Therapeutic Target in Gastric Cancer

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1. Introduction

Globally, gastric cancer ranks to be the 5th most common cancer & 3rd leading cause of death [1]. As the disease presents with non specific early symptoms, it is often diagnosed in the advanced stages. In un-resectable cases, chemotherapy remains alternative line of treatment which might follow in recurrence of the disease. Recent advances assures us newer targeted therapies for better survival of gastric cancer patients. One such molecular target in limelight is Human Epidermal Growth Factor Receptor.

2. Cell Signaling

Her-2 is a protein encoded by proto-oncogene *C-erbB2*, located on chromosome 17q21. It belongs to Her family and is associated with cell growth (**Figure 1**). Over expression of Her-2 supports abnormal cell growth, cell survival and hence promotes malignant transformation.

3. Scoring of Her-2 Expression in Gastric Adenocarcinomas

Various techniques including immunohistochemistry (IHC) and Fluorescent in situ hybridization (FISH) is being used to study Her-2 expression. Researchers observed a vast variability of Her-2 expression in gastric adenocarcinomas. Hence, in order to reduce intra observer variability & to achieve consistency in results, Hofmann Validation Scoring is proposed which is based on IHC (**Table 1**) [4]. This scoring is assimilated by College of American Pathologist (CAP) & Food and Drug administration (FDA) [5].

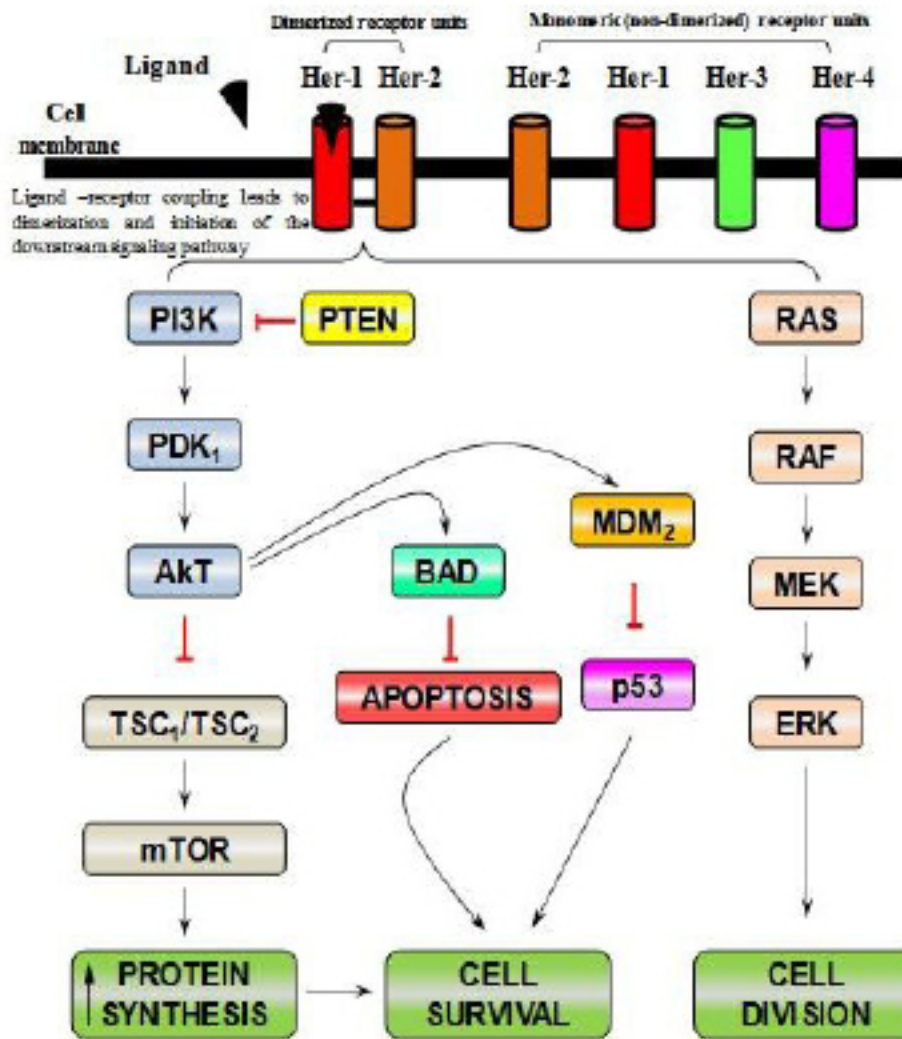


Figure 1: Her family of proteins consists of four structurally related receptors Her-1, Her-2, Her-3 and Her-4. When a ligand (usually a growth factor) binds with these receptors, they dimerize with each other resulting in phosphorylation of intracellular portion of these receptors and activate different pathways. PI3K/AKT a pro-survival pathway, BAD an antiapoptotic protein and MAPK through RAF, RAS, and MAP2K/MEK & ERK leads to survival & proliferation of cells [2, 3]. Her=Human epidermal growth factor; PI3K/AKT=Phosphoinositide 3-kinase; PDK1=Pyruvate dehydrogenase kinase; TSC=Tuberous sclerosis; mTOR=Mammalian target of rapamycin; PTEN= Phosphatase & tensin homolog; BAD=Bcl2 associated death promoter protein; MDM2=Mouse double minute 2 homolog; p53=Tumor suppressor gene; RAS=Rat sarcoma; RAF= Rapidly accelerated fibrosarcoma; MEK=Mitogen activated protein kinase; ERK=Extracellular signal regulated kinases.

Table 1: Hofmann Validation Scoring [4]

Pattern of staining	% of tumor cells stained	Score
No staining	< 10% / < 5%	0 / -ve
Faint/barely perceptible basolateral membrane stainin	>10% / >5%	1+ / -ve
Weak to moderate complete membrane/basolateral membrane staining	>10% / >5%	2+/equivocal
Strong complete membrane/ Basolateral membrane staining	>10% / >5%	3+ / +

4. Use of trastuzumab in Her-2 positive gastric adenocarcinomas

Trastuzumab is a humanized monoclonal antibody which has affinity and specificity for Her-2. Its mechanism of action includes various modalities including arresting the growth of tumor cells at G₁ phase of the growth cycle and down regulation of Her-2 by down streaming the PI3K cascade pathway [6]. Antibody dependent cellular cytotoxicity (ADCC) is another mechanism by which trastuzumab acts by attracting the immune cells towards the tumor sites [7]. It has shown promising results as a targeted therapy in Her-2 positive breast carcinomas. In order to investigate if trastuzumab can also be used in Her-2 positive gastric adenocarcinomas, a randomized controlled phase 3 trial, the ToGA trial (Trastuzumab with chemotherapy in Her-2 positive gastric cancer) was conducted at 122 centres in 24 countries amongst 3803 gastric adenocarcinoma and gastroesophageal junctional adenocarcinoma patients. Of these patients, 810 patients (22%) were Her-2 positive. The Her-2 positive patients were divided into 2 groups: patients in group I were treated with chemotherapy and trastuzumab while patients in group II were treated with chemotherapy alone. The median survival of the patients for group I was 13.8 months while that for group II was 11.1 months. This corresponded to 26% reduction in death rate of patients treated with trastuzumab and 36% reduction in death rate of patients treated with trastuzumab who expressed high Her-2 receptor. Based on the results obtained from the ToGA trial, trastuzumab has been approved in Japan, USA and Europe for those metastatic gastric adenocarcinomas which show over-expression of Her-2 at a score of 3+ in IHC and a positive score at FISH [8]. Favorable outcomes of trastuzumab with chemotherapy have been stated by few of the case reports. [9,10] More clinical trials are underway to develop and introduce other α -Her-2 drugs to be used in clinical practice for Her-2 positive gastric cancer patients[11].

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Overview on Gastric Cancer

Chapter 5

Role of postoperative chemoradiotherapy in the therapeutic management of adenocarcinomas of the stomach and oesogastric junction

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Abstract

The available data in the literature show that for gastric adenocarcinoma or gastroesophageal junction adenocarcinoma, postoperative chemoradiotherapy improves disease-free survival after surgery with D0 or D1 lymph node dissection (and perhaps D2) as well as in case of positive node or R1 resection. With the publications of perioperative chemotherapy trials, the role of postoperative radiotherapy in the therapeutic arsenal of gastric adenocarcinoma or gastroesophageal junction adenocarcinoma becomes difficult to define. Postoperative radiotherapy is indicated in case of R1 resection.

1. Introduction

Surgery is the reference treatment of resectable forms of gastric adenocarcinomas [1]. The margins of resection constitute an essential prognostic factor [1]. After surgery type R0 and in the absence of adjuvant therapy, the survival rate is only 20 to 30% and that of loco-regional recurrences is 40 to 60% [1]. These recurrences are mainly noted for tumors classified T3 and those accompanied with nodal extension (N +), which is frequent and can reach 80% of cases [1,2]. On the other hand, invaded margins (R1 or R2) are reported in 15 to 30% of cases [1,2]. To improve the results of surgery, adjuvant treatments have been studied [3].

2. Review of the Literature

The Macdonald Randomized Trial (INT0116) compared surgery and surgery followed by radiotherapy and chemotherapy for adenocarcinomas of the stomach and oesogastric junction [4]. The number of assessable patients was 556. All patients had an R0 surgery and a lymph

node dissection (D1 in 36% of cases, D2 in 10% of cases and D0 in 54% of cases). The tumor was classified T3 in two-thirds of the cases, with invaded nodes in 84% of cases. Adjuvant therapy included FUFOL-type chemotherapy (5-fluorouracil-folinic acid) and radiotherapy of the tumor bed and regional lymph node. Total dose was 45 Gy delivered at the rate of 2Gy/fraction, 5 fractions/ week. This irradiation was concomitant with chemotherapy. It was interposed between the second and the third cure. Because of the toxicity, only 64% of the patients had the entire therapeutic procedure. The arm with adjuvant therapy was superior to surgery in terms of the probability of overall survival (50% vs. 41%) and progression-free survival (48% vs. 31%) at 3 years [4]. Two criticisms were made for this trial. The first concerns the quality of surgery. Indeed, several authors consider that by performing a lymph node dissection less than D1, it leaves certainly some invaded nodes in place and therefore the surgery is not complete [4,5]. The second concerns acute toxicity. Indeed, haematological toxicity grade 3 related to chemotherapy was reported in 54% of cases. Grade 3 gastrointestinal toxicity was observed in 33% of cases [4,5].

Updating the results of this trial confirmed the benefit of chemoradiotherapy and its persistence at 10 years [6]. This was observed regardless of the type of lymph node dissection, especially if it was D0 or D1. There was no benefit for women with cancer of diffuse intestinal type [6]. The benefit of postoperative chemoradiotherapy after D1 lymph node dissection was also demonstrated by the Dutch Gastric Cancer Group [7]. In this study, the benefit was significant in terms of local recurrence and not significant for survival. This trial did not reveal benefit from the therapeutic association in case of D2 lymph node dissection. However, in the case of surgical margins of type R1, the probability of survival at 2 years and the rate of recurrence were best with postoperative treatment (respectively 66% against 29% and 6% against 26%) [7]. Kim et al., in their non-randomized comparative study, showed a gain in overall survival and survival without recurrence at 5 years in favor of postoperative chemoradiotherapy for patients with adenocarcinomas of the stomach with D2 lymph node dissection [8]. The Phase III ARTIST Trial Comparing Postoperative Chemotherapy and chemoradiotherapy after surgery (R0) with a D2 lymph node dissection, failed to show a significant difference between the two arms in terms of survival. However, the study of patient subgroups showed in case of invaded nodes an improvement in probability of disease-free survival at 3 years in favor of chemoradiotherapy (71% versus 76%, $p = 0.04$) [9].

A meta-analysis showed the superiority of chemoradiotherapy compared with postoperative chemotherapy in terms of local disease control after surgery with D2 dissection [10].

The data available in the literature thus show that for the adenocarcinomas of the stomach and the oesogastric junction, postoperative chemoradiotherapy prolongs survival without disease after surgery and D0 or D1 and probably D2, as well as in the presence of lymph node invasion histologically proven and in case of invaded resection margins (R1). The benefit of

this treatment is a gain of overall survival for some authors.

With the publications of perioperative chemotherapy trials, the role of radiotherapy in the therapeutic arsenal of gastric adenocarcinomas becomes difficult to specify. Three randomized trials compared perioperative chemotherapy and exclusive surgery, which are the trial of medical research council adjuvant gastric infusional chemotherapy (MAGIC), the trial of the "Federation francophone de cancerologie digestive" (FFCD 9703) trial and the European organization for Research and treatment of cancer (EORTC 40954) [11-13]. The MAGIC trial included 503 patients with unresected non metastatic gastric carcinoma. The study randomized patients to receive perioperative chemotherapy, epirubicin, cisplatin, and fluorouracil (ECF) vs. surgery alone. The chemotherapy consisted of 3 cycles of preoperative and 3 cycles of postoperative treatment. It showed a gain in percentage of resections R0, progression-free survival and overall survival, knowing that only 49.5% of the patients had the three courses of chemotherapy [11]. The trial of FFCD included 224 patients. It showed also significant improvement in the rate of R0 resection, progression and overall survival [12]. The EORTC trial included 144 patients with a T3 or T4 carcinoma, with or without node invasion. These patients had D2 lymph node dissection in 95% of cases. It showed only a significant increased rate of R0 resection [13].

In CROSS trial, patients with potentially resectable esophageal or oesogastric junction cancer (3/4 adenocarcinomas, majority distal esophageal, 11% oesogastric junction) were randomized to preoperative CRT using weekly paclitaxel plus carboplatin plus concurrent radiotherapy (41.4 Gy over 5 weeks) or surgery alone. The R0 resection rate was higher with chemoradiation therapy (92% vs. 69%). At a median follow-up of 32 months, median OS was significantly better with preoperative treatment [14].

A meta-analysis of individual data from 14 trials including patients with adenocarcinoma of the esophagus, stomach or oesogastric junction was published [15]. It studied the impact of perioperative chemotherapy compared to surgery alone and showed a survival gain related to perioperative chemotherapy (32% vs. 23%) [15].

The results of these various trials have led to a change in the therapeutic standards for resectable adenocarcinomas of the stomach and the generalization of the practice of perioperative chemotherapy which has become the reference [16-17]. However, the treatment strategies remain different, depending on the country, especially in Western countries [8,15-17]. The absence of a study comparing perioperative chemotherapy with surgery followed by chemoradiotherapy makes the accuracy of the indication of postoperative chemoradiotherapy difficult at the present time. Nevertheless after surgery of type R1, the authors agree on the need for postoperative radiotherapy [18-19].

Stiekema and al studied a series of 409 patients who underwent R1 surgery for gastric

adenocarcinoma. Forty patients received chemotherapy (according to the Macdonald protocol.) The others did not receive adjuvant therapy. The latter were older (Median of 70 years versus 57 years, $p < 0.001$) and had diffuse adenocarcinoma in 43% of cases (versus 80%, $p < 0.001$). There was no significant difference in pT Nor pN the median overall survival time was 13 months in the absence of postoperative treatment and 24 months in the chemoradiotherapy group ($p = 0.003$) [19]. Trials are under way to clarify the role of radiochemotherapy before or after surgery using peri or preoperative chemotherapy [20-25].

3. Conclusion

Postoperative radiotherapy retains a place in the treatment of adenocarcinomas of the stomach and the oesogastric junction for patients who have not received perioperative chemotherapy if the tumor is stage II or III and the general and nutritional state allows it. It must be discussed in case of N1 stage lymph node invasion after D1 lymph node dissection. The place of postoperative chemo-radiotherapy after a D2 lymph node dissection, remains controversial. Postoperative chemoradiotherapy should be offered to patients who have undergone perioperative chemotherapy in case of invaded surgical margins.

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Overview on Gastric Cancer

Chapter 6

Management of Peritoneal Metastases Originated from Gastric Cancer

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Abstract

Peritoneal Surface Malignancies (PSM) indicate the intraabdominal dissemination of neoplasms to the peritoneal surfaces and are previously was named as peritoneal carcinomatosis. Cytoreductive surgery and intraperitoneal chemotherapy have been introduced to the management of peritoneal metastases (PM) over 30 years. This novel approach became a standard of care for Pseudomyxoma Peritonei (PMP) originated from appendiceal or ovarian cancer, peritoneal metastasis of colorectal cancer and peritoneal mesothelioma. Here, management of PM developed from Gastric Cancer (GC) will be presented using cytoreductive surgery and intraperitoneal chemotherapy applications.

Keywords: Gastric cancer; Peritoneal metastasis; Cytoreductive surgery; HIPEC; Peritonectomy

Definition

Peritoneal Metastasis (PM) of Gastric Cancer (GC) describes the intraabdominal dissemination of gastric neoplasms to the peritoneal surfaces. PM of GC has been considered as a terminal stage of the disease and treated with palliative intent. More recently, cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) have been introduced to treatment of peritoneal metastasis of epithelial carcinomas and peritoneal mesothelioma. Management of PM from GC will be presented using cytoreductive surgery and intraperitoneal chemotherapy applications.

In this novel algorithm, staging laparoscopy is performed. Peritoneal Cancer Index (PCI) is determined preoperatively. When the PCI level is more than 6, laparoscopic Hyperthermic Intraoperative Intraperitoneal Chemotherapy (HIPEC) is performed and intraperitoneal port is placed and are treated with bidirectional neoadjuvant intraperitoneal and systemic chemotherapy (NIPS) for 4-6 cycles to downstage the disease. When the PCI level is less than 6, complete cytoreductive surgery and HIPEC are performed.

The operation is two step process:

1. Surgical Resection of involved organs and peritoneum, then
2. Heated chemotherapy solution is circulated in the abdominal cavity to treat any cancer cells that may remain after surgery.

Thus, aim of this technique is that to treat macroscopic diseases with maximum surgical resections in order to achieve complete cytoreduction and to treat microscopic disease with heated circulated chemotherapy.

Prospective randomized studies are needed to be performed to select the patients who can expect to have a benefit from these complex procedures.

1. Introduction

Gastric Cancer (GC) is the fifth most common cancer and the third most common cause of death from cancer in the world [1]. The curative treatment of choice for GC remains surgery with adjuvant systemic chemotherapy. GC has the highest rate of peritoneal metastasis (PM) among intraabdominal cancers. Approximately 10-20% of patients with Gastric Cancer (GC) are detected to have PM at the time of initial diagnosis [2]. PM is the only site of metastasis in 68.6% of GC cases [3]. PM is detected as a recurrence in 36-45.9% of patients with GC after curative treatment [4,5]. Factors are detected to be associated with PM include tumor stage (T3/T4) [6,7], presence of free cancer cells [8] and lymph node involvement [9], and signet ring cell adenocarcinoma [10].

2. Molecular Background of Peritoneal Metastasis of Gastric Cancer

Spontaneously exfoliated or iatrogenically disseminated endoperitoneal free cancer cells adhere to the surface of intraabdominal organs and walls which are trapped by fibrin and stimulated by growth factors due to the wound healing. This process is called as “Tumor cell entrapment hypothesis” proposed by Sugarbaker [11]. These intraperitoneal seeded nodules become hypoxic and may also become resist to systemic chemotherapy.

Endoperitoneal free cancer cells can also diffuse to the “Milky Spots” which are little cribriform “stomata” present on the peritoneal surface consists of macrophages and B1 cells. Milky spots are localized in the omentum and sub diaphragmatic areas [12]. Endoperitoneal free cancer cells are trapped to the spots and became hypoxic nodule [13].

Molecular mechanism of PM of GC is not clear yet. Chemokines (CXC) and growth factors may play a role in mechanism of PM from GC [14]. CXCR4/CXCL12 axis is involved the PM of GC. Elevated expression of CXCR4 in tumor tissue significantly correlates with occurrence of PM. CXCR4-expressing GC cells are attracted to the peritoneal surfaces where its ligand CXCL12 is overexpressed in these surfaces [14].

3. Treatment of Peritoneal Metastasis of Gastric Cancer

Gastric cancer has the highest incidence of peritoneal metastases in gastrointestinal cancers. The main reason for treatment failure is peritoneal recurrence following curative surgery. PM of GC has been treated with palliative treatment as a consequence of thought that is incurable disease. The prognosis of PM of GC is very poor with a median survival after diagnosis is limited to several months. Once PM occurs, response rate of the tumor is decreased to the systemic chemotherapy [15]. The decreased response rate is attributed to the presence of plasma-peritoneal barrier which isolates the peritoneal cavity from the intravenous chemotherapy [16].

4. Cytoreductive Surgery and hyperthermic intraoperative intraperitoneal chemotherapy

PM has been considered as a loco-regional metastasis of the intraabdominal organs that can be treated with cytoreductive surgery (CRS) and hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC). Intraperitoneal chemotherapy has the advantage of direct exposure of intraabdominal tumor cells to the chemotherapeutic agents while they are small or non-vascularized or free in the peritoneal cavity. Therefore, direct contact of cancer cells to the chemotherapy agents also avoids the high risk of toxicity caused by systemic chemotherapy.

Direct cytotoxic effects of hyperthermia have been demonstrated *in vitro* [17] and also

hyperthermia increases the effectiveness of certain molecules [18].

Complete CRS and HIPEC seems to be the only treatment option to achieve long-term survival for peritoneal metastasis.

Table 1: Effectiveness of CRS and HIPEC in patients with PM of GC

Authors	Number of Patients	Chemotherapy Agents in HIPEC	Morbidity/ Mortality	Survival
Fujimoto et al. (20)	15	MMC	-	7.2±4.6 mo
Yonemura et al. (21)	41	MMC+CDDP	29.3% - 0	28.5% for 3-year
Fujimoto et al. (22)	48	MMC	-	31% for 5-year 25.4 % for 8-year
Hirose et al. (23)	17	Etoposide	35.2% - 5.8%	44.4% vs 15.8% HIPEC vs control group in 1-year
Glehen et al. (24)	49	MMC	27% - 4%	Overall 16% 29.4% in CC-0/1 resection in 5-year
Hall et al. (25)	34	MMC	35% - 0%	45% in CC0/1 resection in 2-year 8% in CC2/3 resections 6.7% for 5 year period
Yonemura et al. (26)	107	MMC+CDDP	21.5%-2.8%	6.7 % for 5-year
Scaringi et al. (27)	26	CDDP	27%-3.8%	15 mo for CC-0 & 3.9 moCC-2 (MS)
Glehen et al. (28)	139	MMC±CDDP Or LOHP±Irinotecan	27.8%-6.5%	13% for 5-year survival 23% for CC-0 resection
Yang et al (29)	RCT (34 pts)	MMC+CDDP	14.7%-0	5.9% for 3 y 23% for CC0/1
Magge et al (30)	23	MMC+CDDP	52.2%-4.3%	50% for 1-year 18% for 3 year
Rudloff et al (31) GYMSSA trial	RCT	LOHP	-	11.3 months for Median OS vs 4.3 months in CT arm

Peritonectomy procedures are performed during surgery to remove the affected peritoneum and to achieve complete cytoreduction. Aim of the peritonectomy and complete cytoreduction is to obtain optimal therapeutic effects of HIPEC. The residual disease is

calculated using completeness cytoreduction (CC) score [19].

5. CC Score Definition

Treatment of PM of GC with cytoreductive surgery and HIPEC is still under the investigation. Several studies suggest that the possible long-term survival in patients with complete cytoreductive surgery. Studies performed to evaluation the effectiveness of CRS and HIPEC in patients with PM of GC are given in time dependent manner in Table-1.

Completeness of cytoreduction is the independent prognostic factor in patients with PM of GC [26,28]. In a systematic review, it has been reported that median overall survival is increased to 15 months in case of complete cytoreduction achieved and 5-year survival is 13% in patients with PM of GC [32]. Phase III randomized study conducted to compare the effects of CRS and HIPEC in patients with PM of GC [29]. They showed that median survival was increased to 11 months in CRS&HIPEC group compared to 6.5 months in CRS alone group. In recent prospective randomized clinical trial GYMSSA study, median overall survival was 11.3 months compared to 4.3 months in CRS alone group even though small number of patients were enrolled the study. There is no survivor in the systemic chemotherapy arm after 11 months. Four out of 7 patients were alive more than 12 months, 2 patients close to 2 years, 1 patient more than 4 years with 2 of these patients are still alive. All survivors had an initial Peritoneal Cancer Index less than 15 and they all had a complete cytoreduction.

These results are promising that outcomes of patients with PM of GC might be increased with CRS&HIPEC and PM of GC can be even cured. Limited extension of the disease and complete cytoreduction seem to be the indication of CRS and HIPEC in these patients with PM of GC [28] .

Today, HIPEC indications are changing through to adjuvant or prophylactic setting in patients with PM of colorectal cancer. In near future, HIPEC indications will be changed for GC cases. This theory is supported by several studies. Approximately 60% of patients with GC involved serosa will develop PM [32]. It has been reported that a potential benefit from intraperitoneal chemotherapy with or without hyperthermia as a complementary treatment to curative surgery [33,34].

Effect of intraperitoneal chemotherapy on peritoneal metastasis developed as a recurrence of resectable gastric cancer has been investigated in several studies (Table-2). Fujimoto et al. [35] reported that HIPEC significantly reduced peritoneal recurrence. Yonemura et al. [36] showed that overall survival is increased up to 61% when HIPEC was added in adjuvant setting to surgery. Kim and Bae [37] published 5-year survival is significantly increased in GC patients with invasion of the serosa when they were treated with HIPEC in addition to surgery.

Table 2: Survival effects of intraperitoneal chemotherapy in adjuvant setting to primary surgery for prevention of development PM in patients with GC.

Authors	Number of Patients CRS&HIPEC vs CRS	Survival	Survival benefit
		2-4- and 8-years CRS&HIPEC vs CRS	P value
Fujimoto et al (35)	141 CRS&HIPEC vs CRS 71 vs 70	2-4- and 8 year survival 88%-76%-62% vs 77%-58%-49%	P=0.03
Yonemura (36)	CRS&HIPEC vs CRS vs Intraperitoneal chemotherapy	5 year survival 61%-43%-42%	p<0.05
Kim and Bae (37)	103 51 vs 52 CRS vs CRS+HIPEC	5-year survival 32.7%- 27.1%	p<0.05

Effects and safety of adjuvant intraperitoneal chemotherapy with locally advanced resectable gastric cancer was investigated in meta-analysis [38]. Patients with gastric cancer were included in this meta-analysis whom were randomly assigned to receive surgery combined with intraperitoneal chemotherapy versus surgery without intraperitoneal chemotherapy. Ten reports were analyzed and there was a trend towards survival improvement with normothermic intraperitoneal chemotherapy ($p = 0.06$), but this effect was not time dependent. There was no significant difference between application of intraperitoneal chemotherapy in early postoperative time and delayed postoperative time. Finally, this meta-analysis indicates that intraperitoneal chemotherapy after resection of advanced Gastric Cancer is associated with improved overall survival with time independent manner. However, increased risk of intra-abdominal abscess and neutropenia are also demonstrated. Sun et al. [39] published the result of meta-analysis on the effects of HIPEC in patients with GC involved serosal surfaces. They reported the significant improvement in survival and decrement in peritoneal recurrence rate in HIPEC group in advanced GC cases. Coccolini et al. [40] published the meta-analysis result that also demonstrated the potential benefit of using HIPEC as an adjuvant treatment to advanced gastric cancer.

6. Intraperitoneal Free Cancer Cells and Its Importance

It is established that presence of peritoneal free cancer cells is associated with depth of invasion of the gastric wall that is also associated with poor prognosis [41]. Presence of free

peritoneal cells are associated with an average survival of 4 months compared to 21 months in patients without positive cytology [42]. Peritoneal cytology is important in staging and management of advanced GC [43].

Even though the cytology is negative in peritoneal washing, peritoneal seeding can be detected with using reverse transcriptase-polymerase chain reaction analysis. Indeed, Fujiwara showed the importance of molecular diagnosis in GC patients with poor prognosis [44]. Approximately two of three patients will have positive with PCR diagnosis while they all are negative in cytological examination and PCR positivity is correlated with short term of overall survival and peritoneal recurrence [45,46].

7. Intraperitoneal chemotherapy plus systemic chemotherapy as neoadjuvant setting in management of Peritoneal metastasis of gastric cancer

Yonemura et al. [26] reported a retrospective study on 107 patients with PM of GC. They have used intraperitoneal cisplatin chemotherapy in neoadjuvant setting and performed cytoreductive surgery and HIPEC to responders. Aim of this study was to evaluate the effects of neoadjuvant intraperitoneal chemotherapy applications prior to surgery and HIPEC on overall survival in patients with PM of GC. They have found that median survival was 15.5 months in the group with complete cytoreduction while 7.9 months in the group with incomplete cytoreduction following neoadjuvant intraperitoneal chemotherapy. And, 5-year survival was 27% in the group achieved complete cytoreduction while 6.7% in patients with incomplete cytoreduction. Yonemura and his group concluded that intraperitoneal chemotherapy combined with systemic chemotherapy in neoadjuvant setting prior to CRS and HIPEC is increased overall survival in the patients with PM of GC when completed cytoreductive surgery was achieved.

Canbay et al. [47] reported the results of evaluation bidirectional induction chemotherapy (bidirectional intraperitoneal and systemic induction chemotherapy (BIPSC) in patients with PM of GC who underwent cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) in neoadjuvant setting. One hundred ninety four patients were treated with BIPSC of these patients, 152 (78.3 %) underwent CRS and the median survival rate was 15.8 months. Multivariate analysis showed that pathologic response to these combined treatment approach ($p = 0.001$), low tumor burden [peritoneal cancer index (PCI) ≤ 6] ($p = 0.001$), and completeness of CRS (CC-0, CC-1) ($p = 0.001$) as independent predictors for a better prognosis.

Finally, they conclude that bidirectional induction chemotherapy in neoadjuvant setting may be performed safely, with acceptable morbidity and mortality, in a specialized unit. Response to this treatment prior to CRS and HIPEC and complete CRS and limited peritoneal disease seem to be essential for better outcomes in patients with PM of GC.

Since then the group hypothesized to improve induction therapy to get better outcomes

in patients with PM of GC. The Peritoneal Surface Oncology Group International (PSOGI) suggested a comprehensive management approach consisting of CRS and HIPEC for the treatment of PM of GC as a curative intent [48]. In this strategy, diagnostic laparoscopy was performed and peritoneal cancer index (PCI) was determined. If PCI level was more than 6, a peritoneal port was placed. Neoadjuvant bidirectional intraperitoneal/systemic chemotherapy (NIPS) was initiated two weeks after laparoscopy. Laparoscopy was performed and PCI level was less than 6, cytoreductive surgery was performed to remove all macroscopically observable disease and HIPEC were added for microscopic residual disease. Then, these patients were treated with adjuvant chemotherapy. Even though the PSOGI published the comprehensive treatment modality with proven efficacy, unfortunately, outcome of these studies are results not completely accepted by all surgeons. Outcomes of randomized clinical trials with large sample size will clarify the exact role of this approach in management of PM of GC.

8. Conclusion

PM of GC has a poor prognosis that has been considered to lethal disease and treated palliative systemic chemotherapy. However, CRS and HIPEC to add the systemic treatment approach can increase overall survival in selected patients. Learning curve for a center to perform CRS and HIPEC is 140-220 cases and for individual surgeons about 33 to 70 cases [48].

9. Recommendations

1. PM of GC should be discussed in multidisciplinary team
2. PM of GC should be considered to manage with CRS and HIPEC in physical fit patients
3. Diagnostic laparoscopy should be performed in each cases of GC
4. If cytology is positive and/or PCI is less than 6 is considered as resectable PM of GC cases, CRS and HIPEC should consider in the management of these patients
5. If PCI is more than 6, laparoscopic HIPEC is performed and ip port is placed and the patients are treated with bidirectional chemotherapy until PCI score is decreased. Then, CC-0 resection and HIPEC are performed in patients with pathological response and PCI level less than 6.
6. Prospective randomized studies are needed to be performed to select the patients who can expect to have an optimal benefit from these complex procedures.

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