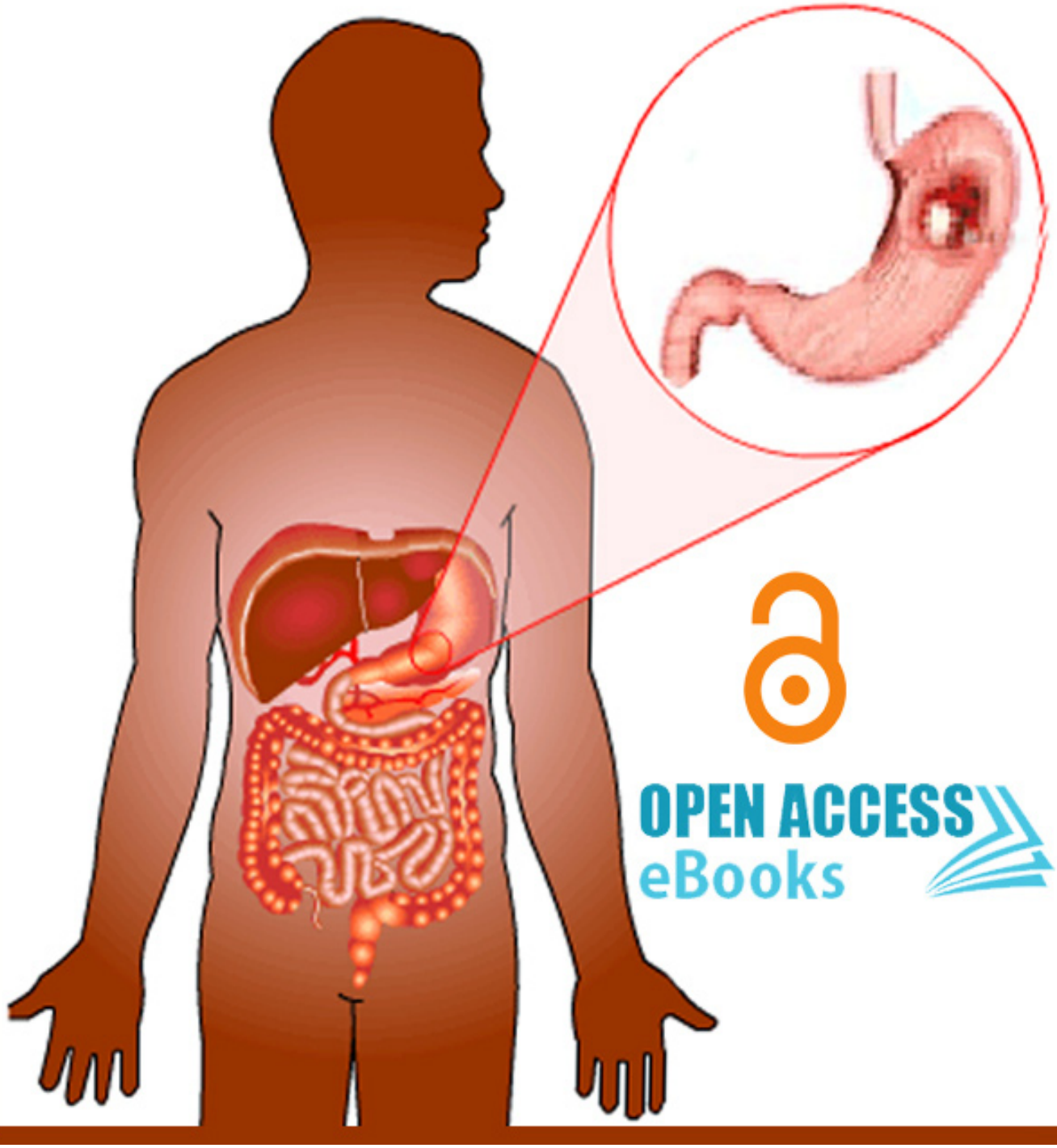
Overview on Gastric Cancer



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Overview on Gastric Cancer

Chapter 1

Targeted Therapy and Immunotherapy

Daniel da Motta Girardi*

Department of oncology, Hospital Sirio-Libanês, Brasília, Brazil.

***Correspondense to: Daniel da Motta Girardi,** Department of oncology, Hospital Sirio-Libanês, Brasília, Brazil.*

Email: danielmgirardi@gmail.com

1. Introduction

Gastric cancer (GC) is the fifth most frequently diagnosed cancer and the third most common cause of cancer-related death globally [1]. The prognosis of GC is poor, especially for patients with metastatic disease, for whom the 5-year overall survival (OS) rate is approximately 5% [2]. For these patients, systemic therapy is the mainstay of treatment, and the goals of this therapy include palliation of symptoms and prolongation of survival.

Systemic treatment with chemotherapy was the first to show a survival benefit over best supportive care (BSC) [3]. Despite some benefit from chemotherapy regimens, including docetaxel, fluoropyrimidines, irinotecan, cisplatin and oxaliplatin, metastatic disease has a dismal prognosis, with a median OS of approximately 11 months for patients not harboring human epidermal growth factor receptor 2 (HER2)overexpression [4].

Over the past several decades, we have witnessed the advent of precision medicine, and remarkable advancements in the fields of targeted therapy and immunotherapy have recently been achieved. Precision medicine involves characterizing the molecular pathways of carcinogenesis and pharmaceutical development of monoclonal antibodies and small-molecule inhibitors that interfere with crucial molecular targets. Successful examples include imatinib for patients with chronic myeloid leukemia [5] and trastuzumab for HER2-overexpressing breast tumors [6].

2. Molecular Characterization of GC

Recent molecular profiling studies have enabled better comprehension of molecular

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pathways in GC. The Cancer Genome Atlas (TCGA) Project performed a comprehensive molecular evaluation of 295 gastric adenocarcinomas and has proposes a molecular classification scheme by which GC is categorized into four subtypes: Epstein–Barr virus (EBV)-positive tumors, microsatellite unstable (MSI) tumors, genomically stable (GS) tumors and tumors with chromosomal instability (CIN) [7]. EBV-positive tumors represent 9% of gastric adenocarcinomas and display recurrent phosphatidylinositol 3-kinase CA (PIK3CA) mutations and amplification of HER2, JAK2 and programmed cell death-ligands 1 and 2 (PD-L1 and PD-L2). The MSI subtype represents 22% of GCs and is prevalent in women and older adults. These tumors are strongly associated with MLH1 promoter hypermethylation, show elevated mutation rates, elevated levels of microsatellite instability and recurrent mutations in PIK3CA, HER3 and HER2. GS tumors are observed in 20% of GC patients, are enriched for the diffuse-type adenocarcinoma and have frequent mutations in RHOA and CDH1. Fusions involving RHO-family GTPase-activating proteins (CLDN18 and ARHGAP26) are also enriched in this subtype, and their fusion products impact RHOA function, which is involved in cell contractility and cellular motility. Finally, the CIN subtype accounts for 50% of gastric adenocarcinomas, is enriched by intestinal histology and shows frequent TP53 mutations and receptor tyrosine kinase (RTK)/RAS amplifications [7,8].

Another notable study sought to identify the most prevalent molecular alterations in GC. The authors identified 22 recurrent focal somatic copy number alterations including known targets such as Fibroblast growth factor receptors 2 (FGFR2) and HER2 but also novel genes such as KLF5 and GATA6. Interestingly, RTK/RAS amplifications were frequent and occurred in approximately 37% of GCs, and KRAS amplifications were also frequent and associated with an adverse prognosis [9].

3. Targeted Agents

Data from systematic profiling studies has revealed numerous molecular alterations in GC. This increased knowledge has significantly improved pharmaceutical development to design and clinically test selective inhibitors against proteins and lipid kinases that play crucial roles in carcinogenesis.

3.1. Anti-HER2 agents

HER2 is a tyrosine kinase member of the epidermal growth factor receptor (EGFR) family. HER2 is involved in the carcinogenesis of many types of cancer and it´s overexpression can be identified in up to 30% of GCs with some differences regarding histological and location characteristics. The overexpression is more common in the intestinal type (34%) than in the diffuse type (6%) and more prevalent in esophagogastric junction (GEJ) tumors (32%) than other locations of stomach (18%) [10,11].

Trastuzumab, a recombinant humanized monoclonal antibody against HER2, was the first targeted agent to be approved for GC in 2010. The approval was based on a phase III trial (ToGA) that evaluated 594 patients with HER2-positive advanced gastric or EGJ cancer. Trastuzumab (8 mg/kg loading dose, then 6 mg/kg every three weeks) was investigated as a first-line treatment in association with chemotherapy consisting of capecitabine plus cisplatin or fluorouracil plus cisplatin administered every 3 weeks for six cycles. The median OS was 13.8 months for thetrastuzumab-plus-chemotherapy arm and 11.1 months for patients in the chemotherapy-alone arm (hazard ratio (HR) 0.74; 95% CI 0.60–0.91; P=0.0046). The response rate (RR) was also higher in the experimental arm (47% versus 35%), as was the median progression-free survival (PFS) (6.7 months versus 5.5 months; HR 0.71; P=0.0002) [11].

Other HER2 blockade drugs were not as successful as trastuzumab. The phase 3 LOGIC trial evaluated the efficacy of lapatinib, a tyrosine kinase inhibitor of EGFR and HER2, as a first-line treatment in combination with chemotherapy (capecitabine plus oxaliplatin). The median OS of the experimental arm was not significantly different from that of the control arm of chemotherapy alone (12.2 versus 10.5 months; HR 0.91; P=0.3492) (check **Table 1** for details) [12]. The TYTAN trial evaluated lapatinib in the second-line setting with paclitaxel. Similar to the LOGIC trial, the median OS was not significantly different (11.0 months for lapatinib and paclitaxel versus 8.9 months for paclitaxel alone; P=0.1044) [13] (**Table 1**). Trastuzumabemtansine (T-DM1) also failed to show survival advantage over standard chemotherapy. The phase III GATSBY trial investigated the efficacy of T-DM1 in patients previously treated for HER2-positive GCs. The median OS was 7.9 months with T-DM1 and 8.6 months with taxane (HR 1.15; one-sided P=0.86) [14] (**Table 1**). Currently, the phase III JACOB trial (NCT01774786) is on going and will evaluate the efficacy and safety of pertuzumab in combination with trastuzumab, fluoropyrimidine and cisplatin as a first-line treatment in participants with HER2-positive metastatic GCs.

3.2. Anti-vascular endothelial growth factor receptor (VEGF) agents

Ramucirumab, a recombinant monoclonal antibody that binds to VEGFR-2, is approved alone and in combination with paclitaxel as a second-line treatment based on two randomized phase 3 trials. The REGARD trial randomized 355 patients, who showed disease progression during first-line platinum-containing or fluoropyrimidine-containing treatment, to ramucirumab-alone (8 mg/kg IV every two weeks) or placebo. The median OS was 5.2 months for the ramucirumab arm and 3.8 months for the placebo arm (HR 0.776; P=0.047). Median progression-free survival was 2.1 months in patients receiving ramucirumab and 1.3 months in those receiving placebo (HR 0.483; P<0.0001). The RR was 3% in both arms [15]. The RAINBOW study compared weekly paclitaxel (80 mg/m^2 on days 1,8, and 15 of each 28-day cycle) plus ramucirumab (8 mg/kg IV every two weeks) to a placebo arm using 665 patients

with metastatic GC or EGJ cancer after first-line platinum and fluoropyrimidine-based combination therapy. The median OS was significantly longer in the ramucirumab arm versus that in the placebo arm (9.6 months versus 7.4 months; HR 0.807; P=0.017) as well as the median PFS (4.4 months versus 2.9 months; HR 0.635; P<0.0001). The RR was also greater in the ramucirumab plus paclitaxel arm (28% versus 16%; P=0.0001) [16].

The benefit of bevacizumab, a monoclonal antibody that binds to soluble VEGF and prevents binding to VEGFR, is uncertain. The AVAGAST trial investigated bevacizumab as a first-line treatment with capecitabine plus cisplatin every 21 days for a maximum of six cycles. Thereafter, capecitabine plus either bevacizumab or placebo was continued until disease progression. There was no significant survival benefit for the experimental arm over the control arm (median OS of 12.1 versus 10.1 months, HR 0.87; P=0.1002), but the median PFS (6.7 versus 5.3 months; HR 0.80; P=0.0037) and overall RR (46.0% versus 37.4%; P=0.0315) were significantly improved [17] (**Table 1**). The AVATAR trial was a phase 3 study, similar to the AVAGAST trial, which was conducted only in Chinese patients. Similar to AVAGAST, the AVATAR trial showed that, compared with the placebo plus chemotherapy, addition of bevacizumab to capecitabine-cisplatin chemotherapy did not improve the median OS (10.5 versus 11.4 months, HR 1.11; P=0.56) [18] (**Table 1**).

Apatinib, an orally active VEGFR-2 inhibitor, was evaluated in a phase 3 Chinese trial that randomized 267 patients with advanced GC or EGJ adenocarcinoma who had progressed through two or more prior lines of chemotherapy. Patients received 850 mg oral apatinib or placebo once daily. The median OS was modestly, but significantly, prolonged (6.5 versus 4.7 months; HR 0.709; P=0.0156), and the median PFS was also improved (2.6 versus 1.8 months; HR 0.444; P<0.001) [19]. Apatinib is approved in China for treatment of advanced GC but is not available in the United States or Europe.

Sunitinib and sorafenib are tyrosine kinase inhibitors (TKIs) that inhibit VEGFR-1, VEGFR-2, and VEGFR-3, as well as other tyrosine kinases. Sunitinib was investigated in a randomized phase 2 trial as a second-line therapy in combination with docetaxel. The primary time-to-progression endpoint was not significantly prolonged with the combination therapy compared with docetaxel alone (3.9 months versus 2.6 months, HR 0.77; P=0.206) [20] (**Table 1**). Sorafenib was evaluated in a phase 2 trial in combination with docetaxel and cisplatin as a first-line treatment for metastatic GC or EGJ adenocarcinoma. The median OS was 13.6 months, the median PFS was 5.8 months and the objective RR was noted in 41% of patients [21].

3.3. Anti-EGFR agents

EGFR overexpression occurs in 2.3%-40% of GCs, depending on the study and the methodology used to investigate the overexpression (immunohistochemistry or fluorescence

in situ hybridization) [10]. However, targeted agents against EGFR have had disappointing clinical outcomes. The phase 3 EXPAND trial evaluated cetuximab, a chimeric monoclonal antibody against EGFR, in a first-line setting with chemotherapy (capecitabineand cisplatin). The median PFS (primary endpoint) was 4.4 months for chemotherapy plus cetuximab and 5.6 months for patients in the chemotherapy-alone arm (HR 1.09; P=0.32) [22] (**Table 1**). Similarly, the REAL3 trial enrolled patients in a first-line setting for chemotherapy (epirubicin, oxaliplatin, and capecitabine) with or without panitumumab (a fully human monoclonal antibody against EGFR). The median OS, which was primary endpoint, was 8.8 months for chemotherapy plus panitumumab versus 11.3 months for the chemotherapy-alone arm (HR 1.37; 95%; P=0.013) [23] (**Table 1**).

3.4. PI3K/AKT/mTOR pathway inhibition

PI3K/AKT/mTOR is one of the most frequently activated pathways in human cancer and is activated in up to 60% of GCs [24]. Everolimus, a mechanistic (formerly known as mammalian) target of rapamycin (mTOR) inhibitor, was investigated in a phase 3 trial (GRANITE-1) in which 656 patients were randomized to the everolimus (10 mg daily) or placebo group after progression to one or two lines of systemic chemotherapy. The median OS was not significantly different (5.4 months for the everolimus arm versus 4.3 months for the placebo arm, HR 0.90; P=0.124), and the median PFS was modestly improved (1.7 months for the everolimus arm versus 1.4 months for the placebo arm, HR 0.66; P<0.001) [25] (**Table 1**). Currently, another phase 3 trial is investigating everolimus in a second-line setting in association with paclitaxel (NCT01248403).

Several other drugs that target the PI3K/AKT/mTOR pathway are under investigation. AZD5363, an AKT inhibitor, is being investigated in two phase 2 trials in combination with paclitaxel as a second-line treatment for patients with GC harboring a PIK3CA mutation (NCT02451956) and in biomarker-negative (PIK3CA/MEK/RAS/TP53/MET) patients (NCT02449655). Another randomized phase 2 trial is investigating the efficacy of GDC-0068, another AKT inhibitor, in combination with modified FOLFOX6 in a first-line scenario (NCT01896531). Finally, a phase IB, dose escalation study, is evaluating the PI3K inhibitor BYL719 in patients with GCs harboring a PIK3CA mutation or HER2 amplification (NCT01613950).

3.5. c-MET inhibitors

Mesenchymal-epithelial transition (MET) receptor amplification or overexpression occurs in 0-23% of GCs [21]. c-MET inhibitors have been tested in GC patients with disappointing results. Two phase 3 trials investigated the safety and efficacy of rilotumumab, a monoclonal antibody against c-Met. RILOMET-1 and RILOMET-2 were designed to test rilotumumab in combination with chemotherapy as a first-line treatment. Both trials were closed in Novem-

ber 2014 based on an increase in the number of deaths in the rilotumumab and chemotherapy arms [26]. MET Gastric was another phase 3 trial that evaluated onartuzumab, a monovalent anti-MET antibody; enrollment was halted early due to the negative results in a phase 2 trial. The analysis of the 592 patients enrolled failed to show the benefit of onartuzumab associated with mFOLFOX6 in the first-line scenario [8]. Foretinib and tivantinib, TKIs against c-MET, also failed to show sustained activity in GC patients in phase 2 trials [8].

3.6. Fibroblast growth factor receptor blockade

Fibroblast growth factor receptors (FGFR1-4) are transmembrane tyrosine kinase receptors that play important roles in carcinogenesis by regulating angiogenesis, cell proliferation, migration and differentiation. FGFR2 amplification is evident in approximately 5% to 10% of GC tumors and is associated with a poor prognosis [27,28].

AZD4547 is a selective FGFR1-3 inhibitor that has been evaluated in comparison with paclitaxel in a randomized phase 2 trial (the SHINE study) as a second-line treatment for GC patients with FGFR2 polysomy or gene amplification. The PFS analysis did not show any statistically significant differences between the two arms [29]. Dovitinib is an oral multitargeted TKI that targets FGFR1-3. A phase 2 trial is ongoing and evaluating dovitinib monotherapy as a salvage treatment in patients with metastatic GC harboring FGFR2 amplifications (NCT01719549). Another phase I/II study is evaluating dovitinib in association with docetaxel as a second-line treatment (NCT01921673).

3.7. Poly-ADP ribose polymerase (PARP) inhibition

PARP, together with the ataxia telangiectasia (ATM) protein, plays an essential role in the DNA damage response [30]. Low ATM protein expression is evident in approximately 13% to 22% of tumors from patients with GC and is correlated with sensitivity to PARP inhibition [30,31]. Olaparib is a PARP inhibitor that was investigated in a randomized phase 2 trial in which olaparib plus paclitaxel was compared with paclitaxel alone in a population of recurrent or metastatic GC patients whose disease had progressed after first-line chemotherapy; the population was enriched with patients with low or undetectable ATM levels. A total of 124 patients were enrolled and the median PFS (primary endpoint) was not significantly different between the two arms (3.91 months for olaparib and paclitaxel arm and 3.55 months for paclitaxel alone arm; P=0.131). However, the median OS was significantly improved in the overall population of the study in favor of the combination arm (13.1 versus 8.3 months, HR 0.56; P=0.005), and the results were even more pronounced in the population with low ATM levels (not reached versus 8.2 months, HR 0.35; P=0.002) [32]. A phase 3 trial is ongoing to evaluate this combination in the second-line setting (NCT01924533).

3.8. Claudin 18.2

Claudins constitute a family of proteins that participate in controlling the flow of molecules between cellular tight junctions. Isoform 2 of the tight junction molecule claudin-18 (CLDN18.2) is frequently expressed in GCs and is involved in carcinogenesis [33]. Claudiximab is a chimeric monoclonal antibody against CLDN18.2 [34]. The FAST trial, a phase IIb trial, evaluated the role of claudiximab in association with chemotherapy in the first-line scenario. A total of 161 patients with GC and EGJ tumors who were claudin-18.2 positive by immunohistochemistry were randomized to receive the EOX regimen (epirubicin 50 mg/m^2, oxaliplatin 130 mg/m^2 d1, and capecitabine 625 mg/m^2 bid, d1–21, every 21 days) with or without claudiximab (loading dose 800 mg/m^2, then 600 mg/ m^2 d1, every 21 days). The study met its primary endpoint with a median PFS of 7.9 months for the experimental arm versus 4.8 months for the chemotherapy-alone arm (HR 0.47; P=0.0001). The median OS was also significantly higher for the claudiximab arm (13.3 versus 8.4 months; HR 0.51; P<0.001) [34]. Future phase 3 trials evaluating the role claudiximab for GC patients are expected.

Table 1: Gastric cancer targeted therapy - Negative trials

Study	Phase	Line	N	Investigational arm	Control arm	RR	PFS	OS
LOGIC	3	First	545	Lapatinib + capecitabine and oxaliplatin	capecitabine + oxaliplatin	53% vs 39%; P=0.0031	6.0 vs 5.4 months; P=0.0381	12.2 vs 10.5 months; P=0.3492
TYTAN	3	Second	261	Lapatinib + paclitaxel	Paclitaxel	27% vs 9%; P<0.001	5.5 vs 4.4 months; P=0.244	11.0 vs 8.9 months; P=0.1044
GATSBY	3	Second	345	T-DM1	Taxane	20.6% vs 19.6%; P=0.8406	2.7 vs 2.9 months; P=0.31	7.9 vs 8.6 months; p=0.86
AVAGAST	3	First	774	Bevacizumab + capecitabine+ cisplatin	capecitabine+ cisplatin	46.0% vs 37.4%; P=0.0315	6.7 vs 5.3 months; P=0.0037	12.1 vs 10.1 months; P=0.1002
AVATAR	3	First	202	Bevacizumab + capecitabine+ cisplatin	capecitabine+ cisplatin	41% vs 34%; P= 0.35	6.3 vs 6.0 months; P=0.47	10.5 vs 11.4 months; P=0.56
Lee, et al	2	Second	107	Sunitinib + docetaxel	Docetaxel	41.1% vs 14.3%; P=0.002	3.9 vs 2.6 months; P=0.206	8.0 vs 6.6 months; P=0.802
EXPAND	3	First	904	Cetuximab + capecitabine + cisplatin	capecitabine + cisplatin	30% vs 29%; P=0.77	4.4 vs 5.6 months; P=0.32	9.4 vs 10.7 months; P=0.95
REAL3	3	First	553	Panitumumab + epirubicin, oxaliplatin, and capecitabine	epirubicin, oxaliplatin, and capecitabine	46% vs 42%; P=0.42	6.0 vs 7.4 months; P= 0.068	8.8 vs 11.3 months; P=0.013

GRAN-ITE-1	3	Second or third	656	Everolimus	Placebo	4.5% vs 2.1%	1.7 vs 1.4 months; P< 0.001	5.4 vs 4.3 months; P=0.124

Abbreviations: RR = response rate; PFS = progression-free survival; OS = overall survival

4. Immunotherapy agents

Immunotherapy is already a reality in oncology and has achieved outstanding results in many cancer types [35-37]. The mechanisms involved in the immune suppression by the tumor are complex. The programmed cell death 1 protein (PD-1) and its ligands (PD-L1 and PD-L2) are key factors that control the ability of tumors to evade the immune surveillance [38]. Similarly, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) negatively regulates T-cell effector responses and is implicated in tumor immunological evasion signature [39]. Currently, several immunotherapy agents that address this mechanism are being tested as treatments for GC patients.

4.1. Pembrolizumab

Pembrolizumab is an anti-PD1 monoclonal antibody. The phase 1b KEYNOTE 012 trial has evaluated 39 patients with PD-L1-positive gastric or EGJ tumors who received pembrolizumab (10 mg/kg every two weeks). This trial has shown manageable toxicities and promising results with 22% of patients achieving an overall response [40]. Early results of the KEYNOTE-059 trial were presented at the 2017 annual meeting of the American Society of Clinical Oncology (ASCO). Cohort 1 comprised 259 patients (not selected by PD-L1 status) who had progressed on ≥2 prior chemotherapy regimens and received pembrolizumab 200 mg every three weeks. The RR was 11.2% in the entire cohort and 15.5% for patients with PD-L1-positive tumors. Grade 3-5 treatment-related adverse events (AEs) occurred in 17% of patients [41]. In cohort 2, the safety and efficacy of pembrolizumab (200 mg every three weeks) plus chemotherapy (cisplatin 80 mg/m^2 + 5-FU 800 mg/m^2 or capecitabine 1000 mg/m^2 every three weeks) as a first-line treatment was evaluated. A total of 25 patients were enrolled with an RR of 60%, a median PFS of 6.6 months and a median OS of 13.8 months. Grade 3-4 treatment-related AEs occurred in 76% of patients in this cohort [42].

Future trials will further clarify the role of pembrolizumab in the treatment of metastatic GC patients. The ongoing phase 3 KEYNOTE-061 trial is evaluating pembrolizumab versus paclitaxel as a second-line treatment (NCT02370498), and the phase 3 KEYNOTE-062 is evaluating pembrolizumab associated with cisplatin plus 5-FU as a first-line treatment (NCT02494583).

4.2. Nivolumab

Nivolumab is another anti-PD1 monoclonal antibody with promising results in GC. The phase 1/2 CheckMate 032 study evaluated nivolumab with or without ipilimumab in heavily pretreated patients with gastric, esophageal or EGJ cancers. Updated results were presented at the 2017 ASCO Annual Meeting. The study evaluated three cohorts: 59 patients received 3 mg/kg nivolumab every two weeks, 49 patients received 1 mg/kg nivolumab plus 3 mg/kg ipilimumab every three weeks (N1 + I3) and 52 patients received 3 mg/kg nivolumab plus 1 mg/kg ipilimumab (N3 + I1). In the nivolumab-alone cohort, the RR was 12%, and the median OS was 6.2 months [43].

The results from a phase 3 trial that evaluated nivolumab as a salvage treatment in 493 patients with gastric and EGJ cancers were presented at the 2017 ASCO Gastrointestinal Cancer Symposium. All patients had failed two or more previous chemotherapy regimens and were randomized to receive nivolumab 3 mg/kg or placebo every two weeks. The median OS was 5.32 months for the nivolumab arm versus 4.14 months for the placebo arm (HR 0.63; $P<0.0001$). The RR was also significantly better for the nivolumab arm (11.2% versus 0%; $P<0.0001$), as was the median PFS (1.61 months versus 1.45 months, HR 0.60; $P<0.0001$). Grade 3 or higher treatment-related AEs occurred in 11.5% of patients in the nivolumab arm [44].

4.3. Ipilimumab

Ipilimumab is a monoclonal antibody that targets CTLA-4. A phase 2 study evaluated the safety and efficacy of ipilimumab versus BSC for patients with advanced gastric or EGJ cancers as a second-line treatment. Fifty-seven patients were randomized to 10 mg/kg ipilimumab every 3 weeks for four doses versus BSC. Immune-related PFS, the primary endpoint, was not improved (2.92 months for ipilimumab versus 4.90 months for BSC, HR 1.44; $P=0.09$) [45].

As described above, the CheckMate 032 trial investigated the efficacy of nivolumab plus ipilimumab. The RR was 24% in the N1 + I3 cohort and 8% in the N3 + I1 cohort. The median OS was 6.9 months for the N1 + I3 patients and 4.8 months for the N3 + I1 patients. Grade 3–4 treatment-related AEs were higher for the N1 + I3 cohort than those for the nivolumab-alone patients and N3 + I1 patients. For example, grade 3-4 diarrhea was observed in 14% of patients in the N1 + I3 cohort and in only 2% of patients in the other two cohorts [43]. The phase 3 CheckMate 649 trial is currently recruiting metastatic gastric or EGJ cancer patients with or without PD-L1 expression to evaluate the efficacy of nivolumab plus ipilimumab versus oxaliplatin plus fluoropyrimidine as a first-line treatment (NCT02872116).

4.4. Avelumab

Avelumab is a monoclonal antibody against PD-L1. The phase 1b JAVELIN trial analyzed a cohort of patients with gastric and EGJ tumors. Patients received avelumab as first-line maintenance or a second-line treatment. A total of 151 patients received avelumab (10 mg/kg IV every two weeks). An unconfirmed response was observed in 9.0% of patients in the maintenance group and in 9.7% of patients who received the medication as a second-line treatment. The disease control rate was 57.3% and 29.0%, and the median PFS was 12 weeks and 6 weeks for the first-line maintenance and second-line treatment groups, respectively. Grade 3 or higher treatment-related AEs were observed in 9.7% of patients [46]. These results led to the development of phase 3 trials addressing avelumab as a first-line maintenance therapy (NCT02625610) and as a third-line treatment (NCT02625623) for metastatic gastric and EGJ cancers.

5. Abbreviations

GC: Gastric Cancer; OS: Overall Survival; BSC: Best supportive care; HER2: Human Epidermal growth factor Receptor 2; TCGA: The Cancer Genome Atlas; EBV: Epstein–Barr vírus; MS: Microsatellite unstable; GS: Genomically stable; CIN: Chromosomal instability; PIK3CA: Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; JAK2: Janus kinase 2; PD-L1: Programmed death-ligand 1; PD-L2: Programmed death-ligand 2; RHOA: Ras homolog gene family, member A; CDH-1: Cadherin-1; RTK: Receptor tyrosine kinase; FGFR2: Fibroblast growth factor receptor 2; KLF5: Krueppel-like factor 5; GATA6: GATA Binding Protein 6; KRAS: Kirsten rat sarcoma viral oncogene homolog; HR: Hazard ratio; RR: Response rate; PFS: Progression-free survival; EGFR: Epidermal growth factor receptor; T-DM1: Trastuzumabemtansine; VEGFR: Vascular endothelial growth factor receptor; EGJ: Esophagogastric junction; mTOR: Mechanistic target of rapamycin; ERK: Extracellular signal-regulated kinases; MET: Mesenchymal-epithelial transition; TKI: Tyrosine kinase inhibitors; PARP: Poly-ADP ribose polymerase; ATM: Ataxia telangiectasia; PD-1: The programmed cell death 1 protein; CTLA-4: Cytotoxic T-lymphocyte-associated protein 4; ASCO: American Society of Clinical Oncology

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Chapter 2

Surgery of Localized Gastric Cancer

Rosa Marti Fernandez*; Leticia Perez Santiago; Roberto Marti Obiol; Fernando Lopez Mozos

Oesophaogastric Unit, Hospital Clinico Universitario de Valencia, Spain

****Correspondence to: Rosa Marti Fernandez**, Oesophaogastric Unit, Hospital Clinico Universitario de Valencia, Spain*

Email: rosamartifernandez@gmail.com

1. Introduction

Gastric carcinoma is one of the most common cancers and one of the most frequent causes of cancer death worldwide. The first step for a correct treatment in gastric cancer is to stage correctly the tumor, based on the TNM classification, in accordance with the classification of the American Joint Committee on Cancer (AJCC) staging system [1].

The correct staging allows us to identify early or initial gastric tumors and choose the adequate treatment for each patient. This factor is one of the most important elements in the improvement of the results in the treatment of gastric cancer.

Once we have diagnosed our patient, through endoscopy and biopsy, we need to practice a TC scan in order to rule out the presence of metastasis. If we discard the presence of metastasis, we must assess the penetration of the tumor in the gastric wall (T) and the involvement of locoregional lymph nodes (N).

The endoscopic ultrasound (EUS) is the most common test for the determination of the T stage, even though its accuracy to distinguish the affectation of the mucosa and submucosa is low and its reliability decreases in case of ulcerated early gastric tumors [2,3,4]. However, it is the elected test in order to determine the T stage of the tumors.

As for the study of the T component, the most common test for the study of the N involvement is the endoscopic ultrasound. The EUS reaches a specificity of 80 % to determine affected or positive perigastric nodes [5].

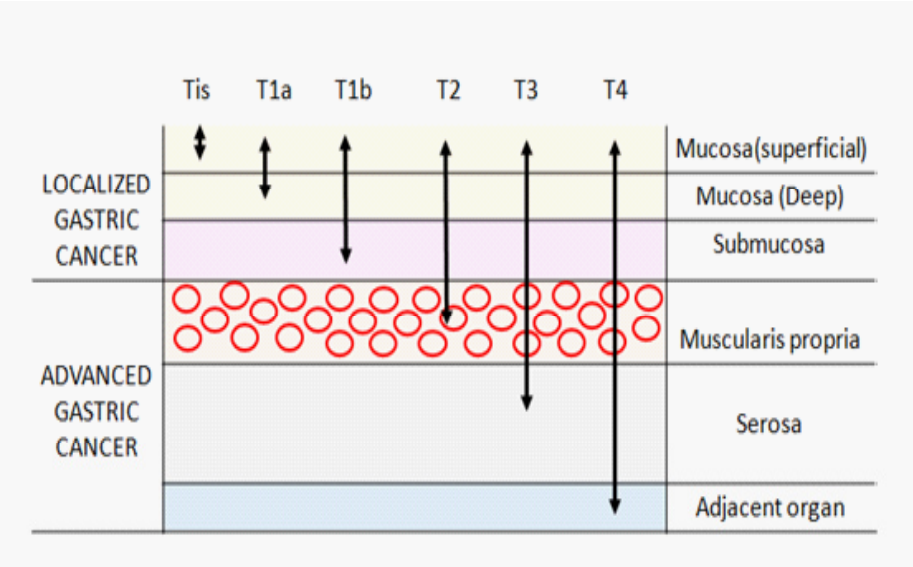
The presence of locoregional lymph nodes metastasis is one of the principle prognostic

factors in gastric cancer [6,7].

If the tumor is intraepithelial the probability of lymph node involvement is nearly absent. If the tumor affects only the mucosa the risk is <3 % but when the submucosa is affected, this risk arises up to 20 % approximately [8,9,10].

There are several characteristics of the tumors that allow us predict or determine the probability of presenting positive lymph nodes. Thus, tumors smaller than 3 cm, non-ulcerated, and without lymphatic infiltration have a minimal probability of lymph node involvement [11].

Grades of affectation on gastric wall



Once we have staged our tumor we define the localized gastric cancer (LGC) as the one that affects the mucosa or submucosa without evidence of involvement of locoregional lymph node metastasis. The involvement of the gastric wall in these cases corresponds to the stages Tis, T1 a, and T1 b.

Tumor staging for gastric cancer

Tis or in situ carcinoma or intraepithelial carcinoma: affects the mucosa without exceeding the lamina propria.

T1a: the tumor involves the lamina propria or the muscularis mucosae.

T1b: the tumor invades the submucosa.

Once classifying the tumor as a localized gastric cancer, the available treatment possibilities are reflected below. The choice of the best option will be based on the characteristics of each patient and tumor.

Therapeutic Possibilities	Conventional surgery or laparoscopic surgery Total or partial gastrectomy Pylorus-preserving gastrectomy Atypical gastrectomy, local resection Endoscopic techniques Endoscopic mucosal resection Endoscopic submucosal dissection Ablative mucosal techniques

2. Surgery Treatment

The main and curative treatment of gastric cancer is surgery [12,13,14]. The morbidity and mortality rates of gastrectomy for gastric cancer vary according to different regions of the world. In countries like Japan or Korea the morbidity and mortality rates round values over 17-20 % and 0.6-0.8 %, respectively, while in Western countries these rates reach values over 40 % and 10 % respectively [13]. This is due to the high incidence of this pathology in the Eastern countries (specially in Japan and Korea), where they have implemented screening programs, so the diagnosis is made at earlier stages increasing the chance of survival; the patients are younger with less comorbidities and the specialization of the surgeons in this pathology.

Surgery Options	Conventional surgery or laparoscopic surgery Total or partial gastrectomy Pylorus-preserving gastrectomy Atypical gastrectomy, local resection Endoscopic techniques Endoscopic mucosal resection Endoscopic submucosal dissection Ablative mucosal techniques

The primary objective of surgery is to achieve the complete removal of the tumor with free disease margins to avoid relapse or local recurrences. In reference to the security disease margins to adopt there are different options. Although in the Japanese Gastric Cancer Treatment Guidelines they advocate in differentiating the security disease margins according to the stage of the patient, in T1 tumors they recommend a security disease margin of 2 cm and in ≥ T2 tumors they recommend a security disease margins of at least 3 cm. In addition, according

to the histological type of the tumor, in intestinal type tumors they support a security disease margin of at least 3 cm while in the diffuse histological type support a margin of 5 cm [15]. Other authors such as Griffin et al, state that a security disease margin of 5 cm is enough without making distinctions according to the histological type or the stage of the tumor [16].

2.1. Conventional Gastrectomy

The choice of the type of surgery is based on the location of the tumor, the characteristics of the tumor, and the characteristics of the patient. The standard worldwide accepted treatment is gastrectomy with D2 lymphadenectomy.

In tumors located in the third distal of the stomach, we must perform a partial gastrectomy with removal of the first duodenal portion.

In tumors located in middle third of the stomach, the therapeutic option will differ according to the remnant stomach on the upper third, being the total gastrectomy the most typical option.

Finally, for tumors located in the upper third the most common option is a total gastrectomy. To avoid performing a total gastrectomy, we can practice a partial gastrectomy with an esophageal-gastric reconstruction; this option has positive oncological results but poor results in terms of quality of life (high rate of gastroesophageal reflux and alkaline reflux). These complications can be offset with a jejunal isoperistaltic interposition [17] or with the performance of a duodenal switch [18].

Numerous authors have studied differences in quality of life, delayed gastric emptying, frequency of appearance of dumping syndrome, weight loss after surgery or symptoms of dysphagia between partial and total gastrectomy, with favorable results in all aspects for the partial gastrectomy group [19,20]. Some works report a higher incidence or local recurrence after a partial gastrectomy [21,22,23].

The improvement of the diagnosis tests that allows us to discard the presence of lymph node metastasis and the diagnosis in earlier stages have permitted the development of the function-preserving gastrectomy that offers a better postoperative quality of life [24]. The function-preserving gastrectomy includes the pylorus-preserving gastrectomy (PPG), proximal gastrectomy, and limited gastrectomy with sentinel node [25].

2.2. Pylorus-Preserving Gastrectomy

The pylorus-preserving gastrectomy was described in 1967 by Maki. It was a surgery indicated for ulcers that later extended to early gastric cancer. It has got some advantages as a decrease of gastric resection, preservation of the pylorus and preservation of the vagus nerve

[20].

The indications for this treatment modality are gastric tumors staged as T1 N0 M0 localized in the middle third with no evidence of lymph node involvement and localized at least 4 cm from the pylorus (despite the fact that it is still a controversial aspect) [27]. This technique is associated with a selective vagotomy, conserving the hepatic branch of the vagus nerve and preserving the infrapyloric and suprapyloric vessels [28].

When we compare the quality of life, frequency of appearance of dumping syndrome, weight loss after surgery or alkaline reflux between patients with pylorus-preserving gastrectomy and patients without preserving the pylorus we find better results in favor of the first group [26,29]. With respect to relapse and 5-overall survival rates, the results are excellent, with 5-year survival rate that reaches values over 96-98% [30,31,32].

2.3. Local Resections

The local resection under laparoscopy seems to be an ideal method to prevent postoperative symptoms caused by gastric resections. They can constitute an alternative to endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) when there are difficult techniques to carry out these procedures. The theoretical advantage over EMR is that local resection is able to achieve a resection of the entire lesion with free macroscopic margins with greater security. In the case of tumors located on the anterior gastric wall or in the curvatures, we can achieve the resection with conventional laparoscopy. In tumors located in posterior gastric wall, we should perform an intragastric laparoscopy or transgastric laparoscopy. A combined technique (laparoscopic endoscopic cooperative surgery) [33] can be helpful for achieving a complete resection of the tumor with adequate margins. The indications defined by Ohgami and colleagues are [34]:

1. Preoperatively diagnosed mucosal cancer.

2. <25 mm diameter elevated lesions.

3. <15 mm diameter depressed lesions without ulcer formation.

2.4. Lymphadenectomy

There is no evidence to prove that the implementation of more extended lymphadectomies in patients with gastric cancer improves survival rates. In fact, an aggressive surgery results in higher rates of postoperative complications [35,36]. The extent of the lymphadenectomy depends on the type of gastrectomy that has been done.

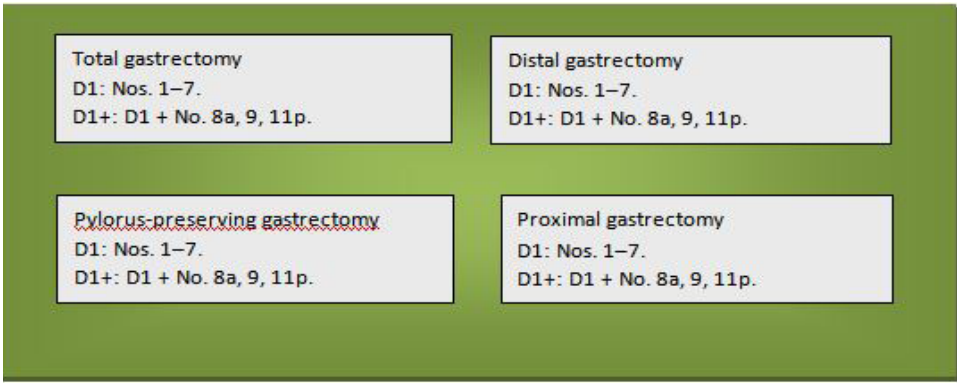
The indications for lymph node dissection according to the Japanese Gastric Cancer Association (JGCA) are the followings [15]:

- D1 lymphadenectomy:

• T1a tumors that do not meet the criteria for endoscopic treatment.
• T1b tumors classified as differentiated type with a diameter of 1.5 cm or less.

- D1+ lymphadenectomy:

• T1N0 tumors that do not meet the criteria for D1 lymphadenectomy.



Lymphadenectomy according to the type of gastrectomy conducted

2.5. Sentinel node

Nowadays, the procedure considered as curative for gastric cancer is gastrectomy associated with lymphadenectomy D2. This surgery has got excellent oncological outcomes but it is not exempt of mid-term and long-term complications. The main problems of the methods of function-preserving gastrectomy (endoscopic treatment or local resection) come from the non-assessment of lymph nodes [37].

The sentinel node technique has been established to avoid unnecessary lymphadenectomy and improve postoperative quality of life [38,39]. The sentinel node is defined as the first lymph node to receive cancer cell drainage. Negative metastasis in the sentinel node indicates no other lymph node metastasis, so it is not necessary to remove more lymph nodes.

Sentinel node mapping and biopsy is performed in patients with:

- T1-T2 tumors and

- Tumors less than 4 cm in diameter and

- N0 tumors.

In patients with positive lymph node metastasis by preoperative image (ultrasonography and tomography) sentinel node technique is not indicated [40]. Actually, sentinel node technique is the best method to evaluate the presence of metastasis in lymph nodes with a detection rate and an accuracy of 97.5% and 99% respectively [41].

We can use combined techniques as the endoscopic full-thickness resection (EFTR) associated to laparoscopic and sentinel node technique; endoscopic mucosal resection or endoscopic submucosal dissection also with the sentinel node technique by laparoscopy or partial resections with sentinel node technique [42,43]. It seems that sentinel node technique correlated with partial resections confer a better quality of life and less postoperative consequences than traditionally distal resections [44].

We dispose of a series of surgical techniques for SN mapping in gastric cancer. We can use a dye or radioisotope colloid (Patent blue, lymphazurin, indocyanine green ICG) to identify the sentinel node. It is injected around the primary tumor, and later, the stained lymph node is identified. Dye guided method is not suitable for patients with a dense adipose tissue [45]. ICG is less visible compared with blue, to overcome this problem, an infrared ray electronic endoscopy (IREE) combined with ICG has been developed with more sensitivity and accuracy [46]. There is also a radio-guided method that uses technetium 99m, for this technique it is necessary to use a gamma probe. This method is better to identify the nodes and can be used in laparoscopic surgery; however, it has got a higher cost.

As we can see, the radio guided method and the IREE have advantages and disadvantages, so a dual tracer method is the best method to obtain a precise identification rate of true sentinel node. Nowadays, SPECT-TC can be used to identify and locate the sentinel node before gastric cancer surgery.

There are two methods to inject the tracer:

- Inject the dye tracer into the submucosal layer around the tumor during an endoscopic examination

- Inject the tracer to the serosa membrane at the site of primary tumor during the surgical procedure.

In relation with the collection method, we can use:

- Picked up method to remove only hot node

- Lymphatic basin dissection (LBD)

There is still controversy about the application of SN mapping in gastric cancer. The results in the literature are divergent. Many authors from Asia report an accuracy of more than 98% in early stages (T1-T2), instead, in Western countries the accuracy is about 80%; this difference may be explained by the difference in the procedural technique. It is still necessary to resolve many issues before this method can be introduced in to daily practice.

2.6. Reconstruction

The modalities of reconstruction after a gastrectomy, whether it is partial or complete, are broad and depend on the initial technique performed. At the moment, there is no ideal technique of reconstruction free of complications or risks associated to surgery. If our initial technique is a total gastrectomy, the available options for reconstruction are Roux en Y reconstruction, double tract method, pouch and Roux en Y or a jejunal interposition. When we compare the different technical options we find that pouch and Roux en Y has got the best results with regard to percentage of intake of food, less incidence of sensation of epigastric fullness, nausea, vomiting, and improvement in nutritional parameters (serum proteins) [47,48].

If we aim for a partial gastrectomy the modality of reconstruction will depend if the resection has been distal or proximal. In the case of proximal resection we can perform an esophageal-gastric anastomosis or practice a jejunal interposition. In the case of a distal resection we dispose of more techniques: Roux en Y reconstruction, jejunal interposition, Billroth I or Billroth II techniques. Finally, if we perform a pylorus-preserving gastrectomy the reconstruction method will be a gastro-gastric anastomosis [15].

The approach method of the surgery may be via laparoscopic, open pathway, open pathway assisted by laparoscopy or robotic surgery. Laparoscopic surgery has a number of advantages over the open pathway such as reduced intraoperative blood less, less postoperative pain, less wound infection rate, lower postoperative ileus, less hospital stay and with equal results with a view to oncological results and number of lymph node dissected but at the expense of a longer operative time. It is considered a safe procedure for the treatment of gastric cancer [12, 49,50].

Robotic surgery permits a better visualization of the abdominal cavity and allows making more precise movements and with a better angle. It has got the same characteristics than the laparoscopic via over the open pathway: reduced intraoperative blood less, lower hospital stay, similar results in order of morbidity and mortality but with a much longer operative time. Long term oncological outcomes have to be determined, there are not randomized controlled trials showing this outcome [51,52].

3. Endoscopic Treatment

As previously mentioned, the indicated treatment for gastric cancer has been classically gastrectomy (either total or partial) associated with the removal of the perigastric lymph nodes. The gastrectomy conditions a serial of long-term alterations that include: dumping syndrome, diarrhea of the vagotomized, weight loss, nutritional alterations (anemia or hypocalcemia). As the majority of localized gastric cancer are presented at a stage without positive regional lymph nodes, new therapeutic modalities of treatment have been developed that are less inva-

sive or aggressive. On account of this, endoscopic techniques have been developed.

The Japanese Gastric Cancer Association (JGCA) established absolute indications for endoscopic treatment and refer to situations with a low probability to present positive lymph node metastasis and in which a tumor block resection can be achieved. These are [15,53]:

1. Differentiated type adenocarcinoma.

2. Absence of ulceration.

3. Diameter ≤ 2 cm.

4. Clinical diagnosis of T 1 a.

There are a number of extended criteria established by the Japanese Gastric Cancer Association that are actually in investigation, must be employed with care in daily clinical practice. These are , :

1. Clinical diagnosis of T 1 a, differentiated type, absence of ulceration, diameter > 2 cm.

2. Clinical diagnosis of T 1 a, differentiated type, presence of ulceration, diameter ≤ 3 cm.

3. Clinical diagnosis of T 1 a, undifferentiated type, absence of ulceration, diameter ≤ 2 cm.

Isomoto et al report that the 5-year survival and disease specific survival rates were 97.1% and 100% respectively in patients treated with ESD in patients meeting the extended criteria [56].

The basis of this therapeutic modality is to achieve an en bloc resection of the tumor, factor that allows us to perform a correct staging of the tumor (establish the degree of tumor invasion, presence of lymphovascular infiltration and determine the degree of tumor differentiation) and set up the necessity of a posterior treatment. Therefore, it has a double aspect: therapeutic and diagnostic, since it allows staging. [15,57,58].

We dispose of three principle endoscopic techniques: endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), and ablative mucosal techniques.

The endoscopic mucosal resection is a procedure in where the lesion is removed until the mucosa layer; there are many technical variants such as the inject and cut, the inject, lift and cut, cap-assisted endoscopic mucosal resection, and endoscopic mucosal resection with ligation. The basis of this procedure consists on the injection of saline solution or serum with epinephrine (diluted 1:100,000) in the mucosa, to achieve a mucosal elevation and posterior removal. In the endoscopic submucosal dissection we make a label in the mucosa around the lesion with glycerol or serum with epinephrine (diluted 1:100.000) mixed with indigo carmin,

then we perform the removal of the lesion with devices that allows us coagulate until de submucosa layer [15,47,59,60,61].

The en bloc rate resection (75.8 % in EMR vs ≥95 % en ESD) and the complete excision of the lesion (73.9 % en EMR vs 90 % en ESD) are higher with the endoscopic submucosal dissection, while the rate of local recurrence is higher with the endoscopic mucosal resection. This depends on the number of histological pieces obtained during the procedure; the greater number of pieces, the greater risk of local recurrence [62,63]. When we compare the survival rates between both procedures there are not differences between EMR and ESD.

The main complications of the endoscopic mucosal resection and the endoscopic submucosal dissection are bleeding and perforation. The most common complication is bleeding (prevalence of 8 % after EMR and 7 % after ESD) that can be classified as early, occurred during the procedure, or delayed, exhibited as melena or hematemesis until the 30 day after the procedure. This complication is more common in tumors located in the distal third of the stomach. Generally it is conservatively managed by endoscopic treatment, coagulating or with endoclips, and surgery is not needed. The perforation rate rises up to 4% after ESD. As in the previous situation occurs, it is usually managed conservatively with placement of endoclips with endoscopy. In this case, the ulceration and the location in the middle third are risk factors [54,56,64].

When we bring into comparison endoscopic treatment (ESD and EMR) with surgery for the treatment of localized gastric cancer, we do not find statistically significant differences in 5-year survival rates (5-year survival rates of 95.7 % and 93.6 % respectively), according to a study published by Choi and colleagues , data that are similar to others published by different authors . Nevertheless, the chance of appearance of a metachronous gastric cancer (defined as the apparition of a new gastric cancer in a different location than the previous one, in an interval of at least one year from the first diagnosis) is higher in the endoscopic group treatment (2.9 – 14 % after endoscopic treatment versus 1.8 – 2.4 % after surgery) . The median hospital stay and the complication rates are higher in patients treated with surgery. [53,61].

The follow-up of these patients should be performed with blood tests (measuring hemogram, biochemistry, liver and kidney function tests, CA 19,9 and CEA), serial endoscopies (twice the first year and annually later) and imaging tests (TC scan) in order to detect relapses. In case of relapse, the treatment can be performed by a new endoscopy or by surgery [61].

Finally, the ablative therapies of the mucosa are a possibility of treatment in cases of tumors located in regions that are difficult to reach with endoscopy and in patients with surgery contraindications due to associated comorbidities [68].

The main disadvantage is the tissue destruction, with no possibility of obtaining a surgi-

cal specimen for an anatomopathologycal study, so the complete destruction of the lesion cannot be verified. Thus, the tumor response should be assessed by new endoscopy and biopsy.

There are many versions of this procedure, being the argon plasma coagulation the most performed, even though other modalities such as Nd:YAG laser and photodynamic therapy exist [69].

When we analyze the complications of the procedure, these are the same as for endoscopic mucosal resection and endoscopic submucosal dissection, bleeding and perforation. The surgical time is lower in comparison to endoscopic mucosal resection. However, the local recurrence rate is higher in patients treated with ablative mucosal techniques than with endoscopic submucosal dissection (3.8 % versus 0.4 % respectively) [62,70,71]. As for the subsequent relapses after this therapeutic option, this can be treated satisfactorily with a new procedure of mucosal ablation, other endoscopic technique or surgery.

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Chapter 3

Surgical Management of Liver Metastases from Gastric Cancer

Fabio Uggeri ; Enrico Pinotti; Simone Famularo; Mattia Garancini; Alessandro Giani; Luca Gianotti; Fabrizio Romano*

Department of Medicine and Surgery, Unit of Hepatobiliary and Pancreatic Surgery, San Gerardo Hospital- University of Milan-Bicocca, Italy

***Correspondenec to: Fabrizio Romano**, San Gerardo Hospital, University of Milan Bicocca, Via Donizetti 106, 20052 Monza, Italy*

Tel: +390392333651, Fax: +390392333651; Email: fabrizio.romano@unimib.it

1. Introduction

Gastric cancer is the fourth most common cancer worldwide and account for 1.5% of all new diagnoses and 5.2% of all cancer deaths [1,2]. More than 139.000 new cases in Europe and more than 951.000 new cases worldwide were diagnosed in 2012. Gastric cancer is often diagnosed at an advanced stage due to the lack of symptoms at an early stage and lack of a screening schedule throughout most of the world. At the time of diagnosis 35% of patients present with evidence of distant metastases and 4-14% have metastatic disease to the liver [3,4]. Furthermore in patients who present with local disease and undergo curative resection, the development of metastases is common, with hepatic metastases the commonest site of recurrence, occurring in over one third of patients [5,6]. The aggressive nature of gastric cancer is the reason why hepatic resection in many cases is not taken into account. Although the effectiveness of liver resection for metastatic colorectal cancer has been already established [7-9], since '90 liver metastases from gastric cancer were considered a non surgical entity. Starting from 2000 reports of hepatic resection for liver metastases of gastric cancer has been published even if rare and till today its significance is still controversial [10]. In fact a number of studies reported that the effect and benefit of hepatic resection for either synchronous or metachronous gastric hepatic metastases (LMGC) on survival was dubious [11]. Furthermore the surgical indications for liver metastases of colorectal cancer have been expanded to include all technically resectable metastases numbering 4 or more [12]. On the contrary, the surgical indications for liver metastases of gastric cancer must be carefully determined because of the more severe

biologic nature of this disease [13].

Most of patients with gastric cancer with concomitant liver metastases are excluded from candidates for curative surgery accompanied with hepatic resection due to incurable simultaneous factor such as peritoneal dissemination, widespread lymph nodal metastases and direct invasion to adjacent structures [14]. In fact LMGC often represent only a part of a generalized spread of the primary tumor ("the iceberg tip"). Furthermore very few patient with LMGC are good candidates for liver surgery due to multiple, scattered, bilobar lesions [15]. Only 0.5-10% of patients with GCLM will have technically resectable disease in the absence of extrahepatic disease. Patients with isolated metastases are unusual, accounting for 0.5% of cases in the Linhares's series [16]. On the other hand metastatic liver involvement, which occurs in up to 50% of patients with gastric cancer, makes long-term survival without treatment impossible, with a median survival of 6 months. These data growth to 7-15 months with chemotherapy schedules. There are no adequate large prospective studies detailing the natural history of metastatic gastric carcinoma and long term survival. However, two small randomized trials compared best supportive care vs. combination chemotherapy and found that no patients treated with supportive care lived for >1 year [17,18]. Survival data for patients with metastatic gastric cancer (MGC) to the liver only are also limited and the prognosis for GC patients with liver metastases is poor with 6 months survival rate of 20-50%. In a study analysing 643 patients enrolled in five separate chemotherapy trials by the Japanese Clinical Oncology Group (JCOG), 5-year survival for patients with metastases confined to the liver and treated with systemic therapy alone was 1.7% [19]. Palliative chemotherapy using various regimens has been widely used as the treatment of choice, and is considered the mainstay of treatment for metastatic disease. There have been several chemotherapy regimens described in the literature for treatment of metastatic disease, but there is currently no consensus as to which regimen provided the best response. Even with systemic chemotherapy only modest improvements in overall survival have been observed, with median survival increasing from approximately 3 months to 7–15 months. Long-term survival is rarely reported [20-22]. In particular, considering the few trials evaluating systemic chemotherapy in the subset of patients with liver-only metastatic involvement, 5-years survival rates do not reach 2% [19]. More recently there has been evidence sustaining a role of biological agents for the treatment of metastatic disease [23]. Baba *et al.* [24] have shown that the outcome for patients with non curative resection for advanced gastric cancer is extremely poor, and the optimal treatment of patients with isolated metastases without peritoneal dissemination remains open to discussion because of the biological, clinical and pathological aggressiveness of gastric cancer. In contrast to the treatment of colorectal liver metastases, there is not yet a standard multidisciplinary therapeutic approach that could have an effect on 5 years survival of these patients. Various studies show that complete surgical resection is the only form of therapy that can be employed with a curative intention. Otherwise the guidelines do not recommend surgery for stage IV gastric cancer;

according to the National Comprehensive Cancer Network Guidelines [25] surgical therapy is not recommended. Liver metastases is still considered a non-curative factor in patients with gastric cancer in classification by both the Japanese Gastric Cancer Association and the American Joint Committee on Cancer Staging. It seems that the clinical community does not include surgery among the therapeutic options for these patients, with an "aprioristic passive attitude" as reported by Tiberio et al. [26]. Although until a few years ago the Japanese Gastric Cancer Treatment Guidelines recommended chemotherapy, radiation therapy or palliative surgery for the treatment of metastatic gastric cancer [27].

Liver resection is now considered a routine procedure at speciality centres around the world: improvements in the understanding of anatomy, physiology, perioperative care and surgical techniques and technologies have reduced operative mortality in most tertiary referral centres to < 2% [28]. Recently it was revised the possibility of surgically removed metastatic lesions in order to obtain radical (R0) resection [29]. The works in literature reports a survival rate at 5-year after surgical resection of hepatic metastases ranging from 0-38% [30], but the lack of clinical trials on hepatectomy for this disease makes it difficult to draw solid conclusions relating on the most important prognostic factors. In the last 17 years several authors have reported on their limited experiences of surgical complete resection of the metastatic tumors in selected patients of LMGC [31-33], considering patients with liver metastases as sole metastatic site. However, considering survival performances extrapolated from a cohort of 1452 patients submitted to hepatic resection for noncolorectal nonendocrine liver metastases, Adam *et al.* [34] observed that metastases from gastric adenocarcinoma performed in an intermediate way, ranking 10th in a list of 18 primaries. Many retrospective case-control series have been reported. Otherwise these analyses are presented from a single centre, have small number of cases and include old cases. The quality of evidence is low with no randomised controlled trials, and most studies including less the fifty patients treated over a prolonged time period. This should reflect the highly selected nature where hepatic resection may be of benefit. to identifying patients. Even with these limitations a recent review of the literature about LMGC report a median 1-3-5 years survival on 436 patients of 62%, 30% and 26.5%, and a median survival of 17 months [35]. So even if the percentage of patients who may benefit from resection is probably small, otherwise only surgery is able to obtain long term survival, with 5 years survival rate up to 30% for metachronous liver metastases and only 6% for synchronous. Considering these data recently the Guidelines Committee of the Japan Gastric Cancer Association reconsidered the treatment of potentially resectable M1 diseases, on the basis of reports that showed favourable results [29]. In the last years several literature revision and meta-analysis has been published, proving the interest on this topic. The goal of this papers was to identify prognostic factor to select patients who could be considered ideal candidate to liver resection and should be offered hepatectomy with survival benefit . In the Long review [36] with approximately 1000 of patients, the overall survival was similar to that achieved for colorectal liver metasta-

ses fifteen years ago (1-3-5 years survival respectively of 68%-31%-27%). Moreover all the review and meta-analysis concluded that hepatic resection is associated with lower mortality and longer median overall survival than palliative treatment for selected patients with GCLM. Martella et al. [37] concluded that even if the percentage of patients who may benefit from resection is probably small, the best survival rate are associated with surgical treatment which should be chosen whenever possible. On the basis of these analysis the change of mind in the approach to GCLM sponsored by Tiberio *et al.* [38] seems to be a matter of fact, and "the seeds planted by a handful of Pioneers begin to grow". Surgical management of hepatic metastases from gastric cancer is becoming one of the hot topics in oncology community. Therefore the importance of liver resection for GCLM must be thoroughly analyzed and the determination of selection criteria for hepatic resection and conditions for long-term survival after hepatectomy for LMGC should be considered as crucial. In fact identification of prognostic factors that predict outcome following surgical resection of gastric hepatic metastases should assist in identification of patients most likely to benefit from this intervention or more importantly, assist in identification of patients unlikely to benefit. We revised the literature regarding monocentric and multi-centric studies, studies focused on synchronous metastases and review or meta-analysis.

1.1. Criteria for resection

Criteria for hepatic resection offered by Okano *et al.* [39] are broadly defined: hepatic resection is indicated in patients (1) with synchronous metastases who have no peritoneal dissemination or other distant metastases and (2) with metachronous metastases, but no other recurrent lesion. Ambiru *et al.* [11] added a third criterion, (3) complete resection of hepatic metastases with acceptable postoperative hepatic function. In a recent report by Roh *et al.* [40], hepatic resection is said to be indicated only in patients with hepatic metastases in one lobe of the liver without peritoneal dissemination, hilar node metastases or distant metastases. Criteria actually accepted for resection of hepatic metastases from gastric cancer are now as follows: 1) good control of the primary tumor and complete resection of primary tumor and lymph nodes involvement in synchronous disease; 2) no signs at preoperative work up of disseminated diseases, hilar lymph nodes metastases, peritoneal dissemination or extrahepatic metastases; 3) complete resection of hepatic metastases (macroscopically no residual tumor). Following these selection criteria Ochiai *et al.* [41] found a hepatic resection incidence of 21 in 6540 patients (0.3%) with a gastric cancer who underwent a gastrectomy. Saiura *et al.* [42] found an incidence of 10 in 1807 similar patients (0.6%), and Okano *et al.* [39] found an incidence of 19 in 807 patients (2.4%). A recent literature review reported only 229 liver resection for LMGC, maybe reflecting an a priori passive attitude toward these patients. Some study report a classification of degree of liver metastases in patients with LMGC according to the Japanese Classification of Gastric Carcinoma [43]: H1: metastases were limited to one of the lobes; H2:

there were a few scattered metastases in both lobes; H3: there were numerous scattered metastases in both lobes.

Independent prognostic factors analyzed in the literature identify a miscellaneous variables that can affect prognosis: unilobar distribution, number of metastatic nodules, presence of Glisson's capsule invasion, tumor size, R0 resection, synchronous or metachronous disease, pseudo-capsule formation and stage of primary tumor. In general hepatic resection is indicated when surgical procedure is not particularly invasive, practiced with radical plans and without evidence of extrahepatic disease [39]. Unfortunately, most hepatic metastases from gastric adenocarcinoma are multiple, bilateral, and combined with peritoneal or lymph nodes metastases, which directly invade adjacent organs precluding a radical surgical approach. The resectability rate is low and about only 20 % of the patients with liver metastases can be treated surgically in a situation where only patients with potentially resectable disease are referred, a situation possibly encountered at the surgical department in high-volume cancer centre [30].

In addition to factors closely associated with the metastatic lesion, the characteristics of the primary tumor are of significant importance in the therapeutic decision. The prognostic aspect of gastric cancer with liver metastases is not well clarified. The detection of liver metastases from gastric cancer occur in approximately 3% to 14% at the diagnosis of primary tumor [44] and in up to 37% of patients following gastrectomy [45]. Some studies compared the effectiveness of the liver resection, even for synchronous lesions, to palliative treatments. Hepatic resection is associated with a significant reduction in mortality at 1 and 2 years [46-48]. Although the data come from non-randomized studies, difficult to perform because of the paucity of patients recruitable, it is undeniable that surgical resection lead to a real benefit in terms of survival compared to those patients treated with chemotherapy alone. Recent chemotherapy protocols for liver metastatic gastric cancer have not yet led to satisfactory results with a median survival of 12 months and 3-year survival rate around 5% without surgery [49].

In many cases clinicians hesitation is associated to the fear that the hepatic resection can affect quality of life, nutritional and physical condition of patient postponing adjuvant chemotherapy. Although the clinical benefit of hepatic resection for metastases from gastric cancer is not widely accepted , several studies confirmed an improvement in prognosis with surgical treatment. A systematic review [36] involving 994 patients showed a median overall survival of 21 months for surgery compared from 11.3 to 13.8 months for patients in a large randomized trial who received only combination chemotherapy [50,51]. Miki *et al*. [52] retrospectively compared, even if in a limited number of patients, three different therapeutic strategies in patients with liver metastases from gastric cancer: gastrectomy plus hepatic resection, palliative gastrectomy and chemotherapy alone and concluded that gastrectomy plus hepatectomy might be a promising treatment options with 5-year survival of 36.7% for resected patients versus 15.4% for palliative gastrectomy and 0% for chemotherapy alone. To date is ongoing in Japan

and Korea a prospective randomized trial that aims to evaluate the role of gastrectomy in the management of incurable advanced gastric cancer. Patients with advanced gastric cancer diagnosed as having a single non-curable factor are randomized to gastrectomy plus chemotherapy or chemotherapy alone. The study includes patients with hepatic metastases till four lesions with a maximum diameter of 5 centimeters [53]. The results of this trial will lead to more solid data.

Hired a possible survival benefit after surgery, carefully assessment of surgical indications it is of crucial importance to clarify the condition of 5-years survival. The actual criteria include the absence of peritoneal or other metastases on pre-operative imaging, adequate physical condition , radical resection of metastases with preserved liver function. Furthermore the presence of a single lesion, disease-free margins, low stage of primary tumor, absence of lymph node or venous invasion appear to be factors that lead to a better prognosis [48]. In addition it must also include the possible response to neo-adjuvant chemotherapy in patients who received it. A progression of disease after therapy can be considered a significant adverse prognostic factor [54].

To date the results in the literature on the treatment of liver metastases from gastric cancer appear in parallel with the results obtained for colorectal liver metastases, but should be viewed with caution [55]. The studies on the topic consist in small institutional series and with patients highly selected. A recruitment of a growing number of patients enrolled to hepatectomy, after a careful multidisciplinary assessment will clarify and confirm the therapeutic role of surgical resection for liver metastases from gastric cancer.

1.2. Assessment of survival outcomes

The effectiveness of hepatic resection has not been well defined. In addition the clinicopathologic characteristic related to the prognosis of gastric cancer with hepatic metastases have not comprehensively identified. Nevertheless the presence of hepatic metastases is a statistically significant poor prognostic factor for patients with gastric cancer [14].

The cumulative survival rate reported in early studies was generally poor, reflecting a generalized disease. Elias et al. showed that the 3-years survival after hepatic resection was less than 20% [56]. In recent series the 1-year survival rate ranged from 42% to 90% and 5-year survival rate from 0% to 38% (see **Table 1**). The long-term results after liver resection for metastases from gastric cancer show a wide range (**Table 1**). Most studies concerning this issue come from Japan and the reported long-term survival rates exceed 30% in some series [8,33,57]. In contrast, in the western study from Zacherl et al. none of the patients survived five years after resection [58]. Otherwise in recent report form western countries the 5 years survival rate was of 19 and 27% [47,59].

Thus, the clinical benefit of resection of hepatic metastases from gastric carcinoma is still not widely accepted. However, non surgical treatments, including systemic or hepatic artery infusion chemotherapy, do not achieve satisfactory results. In patients treated by gastrectomy and chemotherapy, median survival times are reported to range from 2.9 to 11.8 months [60,61].

Furthermore Bines et al. [62] reported one long-term survivor of seven (14.3%) and other series showed 11.1 to 19% long-term survivors. Although few, the long-term survivors after hepatic resection do exist. Therefore to determine the indication of liver surgery is crucial and to clarify the condition of 5-year survivors..

2. Prognostic Factors

An attempt to define criteria for selection of patients with favourable outcome has been previously made in various series. We herein report a comprehensive review of the literature experience of small and selected populations series. We classified the characteristics predictive of good or poor outcome according to the primary tumor, the metastases and the type of surgery (**Table 2**).

2.1. Predictive of outcome related to primary tumor

Ochiai *et al.* have shown how the presence of serosal invasion by gastric cancer is the only significant determinant at synchronous resection and both lymphatic and venous invasion were significant prognostic factors available after histological examination [41]. Therefore the presence of serosal invasion at the time of the primitive resection should be considered a worse prognostic factor in case of synchronous and metachronous metastases, while the presence of positive lymph nodes and microscopic venous infiltration should be taken into account in case of metachronous metastases, as confirmed by the study of Morise *et al.* [63]. Also a recent multicentric Japanese analysis of long-term outcome after surgical resection for gastric cancer liver metastases stressed that the present of serosal invasion of primary gastric cancer is a poor prognostic factor [64]. The serosal invasion of primary GC is the first step in the advancement to peritoneal dissemination and thus considered as a significant poor prognostic factor after GCLM resection. These data were confirmed in the studies of Shinohara, Kostov and Takemura [65-67]. Further more Shirabe showed that lymphatic and venous invasion of cancer cells from primary gastric cancer are clinicopathological prognostic factors of poor outcome at both univariate and multivariate analysis [68]. In a recent paper Sekiguchi et al. analyzed the risk factors associated with lymphatic and venous involvement in patients undergoing endoscopic resection for gastric cancer and concluded that the papillary histology of primary tumor may have a negative prognostic role on neoplastic venous and lymph nodes dissemination. He also reports a case of liver metastases in a patient not subjected to surgical resection [69]. This could give a further confirmation of the worse prognosis for patients

with venous or lymph node tumor invasion also in early gastric cancer, although the data are preliminary and will require confirmation. Other authors emphasized and confirmed that the presence of lymph nodal tumor invasion negatively impacts on prognosis [42,70]. Imamura *et al*. [31] reported the grade of differentiation of the primary tumor as a poor prognostic factor. Koga et al. [57], Takemura *et al.* [67] stated as a serosal invasion (T4) of the primary gastric cancer is an unfavorable prognostic factor after hepatic resection. Also Tiberio *et al.* [71] in a multicentric report supported the fact that the presence of locally advanced gastric lesion (T4) and a non-radical resection in the synchronous setting suggests prudence and probably abstention from hepatectomy. Zacherl *et al.* [58] reported that tumor localization of primary gastric cancer (proximal third versus distal two-thirds of the stomach) was a marginal predictive negative factor for overall survival, while in the study of Tsujimoto *et al.* [72] the gastric cancer size greater than 6 cm was considered a predictor of poor survival. A prospective study found that in patients who underwent hepatic resection combined with the removal of primary gastric tumor, lymph node ratio may have a prognostic role. A high limph node ratio had significantly shorter overall survival than those with low lymph node ratio [73]. Elevated lymph node ratio was significantly associated with advanced pN stage, larger primary tumor size, the presence of microvascular invasion and neoadjuvant chemotherapy [36]. Also the presence of the positive peritoneal washing liquid is considered a negative prognostic factor and several authors reported no benefit in terms of survival following surgical resection [74,75].

However, some studies showed these were not significant prognostic factors and are still controversial. Miyazaki [70] and Okano [39] reported that there was non significant difference in term of depth of invasion or lymph node metastases of the gastric cancer between surviving and non surviving patients. Koga [57] reported a marginal significance of the serosal invasion of the primary tumor. Even in more recent studies with more than 30 cases [76,77] serosal invasion was not considered as a prognostic factor. More over the multi-centric studies from Komeda [78], Markar [55] and Oki [79] not attributed to serosal invasion a prognostic significance.

2.2. Predictive of outcome related to metastases

The analysis of prognostic factors related to metastatic lesion has highlighted among the most important: number of lesions and the status of resection margin has been confirmed in a recent meta-analysis by Markar *et al.* [55].

The number of the metastatic nodules in the liver has been reported to be an important prognostic factor in 18 mono-centric and 3 multi-centric studies. Okano *et al.* [39] reported 3-year survival rates of 56% for single metastases and 0% for multiple metastases, and the number of liver metastases was a significant prognostic factor in other reports as well. In Koga *et al.* [57] and Shirabe *et al.* [68] studies none of the patients with multiple gastric liver metas-

tases (three of more lesions) survived beyond 3 years, whereas the 5 year survival rate for the patients with solitary liver metastases was 55% with eight long-term survivors. Aizawa *et al.* [80] analyzed the prognostic factors of 74 patients undergoing liver resection for synchronous metastases and detected as the presence of a single lesion is the most significant prognostic factor. In fact, dividing the patients into two subgroups "solitary or multiple metastases" the median 5-year survival is 24.2 compared to 12.6 in the second group. Okano *et al.* [39] reported for a group of patients with synchronous and metachronous disease a 3-year survival rates of 56% for single metastases and 0% for multiple metastases, as confirmed a few years later by Ueda *et al.* [81]. Shirabe *et al.* [68] described the presence of three or more tumors as an independent poor prognostic factor according to both univariate and multivariate analysis; moreover, all four patients who survived beyond 5 years in their study also had solitary tumors, and almost all patients described as long-term survivors had a solitary liver metastasis. This data were confirmed in the study of Sakamoto [33] with a survival of 56% for solitary lesions against none long term survivor in case of multiple tumors. In a more recent study Sakamoto [82] showed against the value of solitary lesion adding the unilobar distribution as good predictive factor for survival of patients, as previously reported in the Miyazaki's paper [70]. Recently Schildberg *et al.* [76] and Wang *et al.* [83] confirmed in their studies as a single metastases is a favorable prognostic factor. Schildberg [76] reported a significantly better median survival for single metastases versus multiple metastases (21 vs 4 months) in a large-scale multi-institutional retrospective cohort study with a large sample of 256 patients and Wang [83] In said that a single lesion was a independent favourable prognostic factor at multivariate analysis. Furthermore, Takemura *et al.* [67] also reported good results with a 5-year survival rate and MST of 37% and 34 months, respectively in candidates with three or fewer liver metastases. In some study the number of liver metastases was a marginal prognostic factor for survival after hepatic surgery with curative intent. The favourable survival outcome for patients with a solitary metastasis, which was no worse than that for a solitary metastasis of colorectal cancer, indicates that patients with a solitary metastasis of gastric cancer are good candidates for surgical resection . On the other hand, the surgical indications should be considered more carefully in patients with multiple metastases of gastric cancer than patients with multiple metastases of colorectal cancer.

From the literature seems to emerge the fact that in all cases a long survival patients are carriers of a single lesions. Otherwise, *Saiura et al.* [42] showed two long-term survivors longer than 5 years with more than three metastases concluding that if the curative resection (R0) can be achieved, hepatic resection should not be abandoned even in patients with multiple liver metastases. According to previous paper of Saiura [42], Dittmar *et al.* [47] concluded their study stating that multiple liver tumors and a bilateral spread within the liver could be treated by surgical therapy in strictly selected cases as long as all tumors can be removed curatively. Kinoshita *et al.* [64] reported a series in which some patients underwent surgical liver resec-

tion for three or fewer liver metastases detected at preoperative diagnosis. The results stated that no solitary metastases but 3 or more hepatic tumors was an independent prognostic factor. In the last years Shinohara [65], Tatsubayashi [84] and Ohkura [85] confirmed the role of number of lesions as a prognostic factor. Ohkura [85] reported that hepatectomy offers superior survival compared with non-surgical treatment for <3 metastatic tumors with diameters <3 cm from gastric cancer. Otherwise the indication of tumor size (<3 cm) for hepatic resection is, however, not obligatory since several studies reported favourable prognosis for the patients with tumors 4–5 cm in maximum diameter. Oki *et al.* [79] recently reported that solitary metastasis was an independent prognostic factor in a large-scale multi-institutional cohort study. Moreover in all the other multi-centric studies the number of liver lesions was a predictor of outcome.

As for the lobar distribution of liver metastases, patients with bilobar tumors had a worse outcome than patients with a unilobar tumor, as shown by Zacherl and coll. [58]. Tiberio *et al.* [48] describe as the hepatic involvement (H3) worsened the prognosis of patients in synchronous metastases setting. Also Liu *et al.* [86] confirmed that the extension of liver metastases was an independent significant prognostic factor for poor survival. However, the number and lobar distribution of the tumors were correlated, and so the significance of the lobar distribution of tumors as a prognostic factor should be re-evaluated in larger series. Furthermore the distribution of metastatic lesions in many cases is a discriminating factor in order to obtain a radical resection (R0). R0 resection is mandatory, it must be the goal that the surgeon arises to reach in the pre-operative planning of these patients. Radical resection is a major prognostic factor that impacts significantly on long-term survival.

Moreover several studies take into account the dimension of liver metastases as a possible prognostic factor. Kinoshita *et al.* [64] showed as the patients with more than 3 metastases or lesion larger than 5 cm had a worse prognosis as well as reported by Ohkura [85] for more than 3 lesion of more than 3 cm. The same data were reported in multi-centric analysis of Oki [79] and Kinoshita [64].

Concluding as regard the histologic characteristics of liver metastases from gastric cancer, lymphocytes aggregation, enclosing the metastatic tumor, is reported as a good prognostic factor by Fujii [87]. This could be explained with the favourable action of TILs (tumor infiltrating Lymphocytes) in preventing tumor extension in gastric cancer patients [88]. Okano [39] demonstrated that the presence of a fibrous pseudocapsule around liver metastases is a promising indicator of a better prognosis, being closely associated with patient survival. The paper reported an actuarial 1-year and 3-year survival rates of 87% and 51% for patients with a fibrous pseudocapsule and 57% and 0% for patients without it. Pseudocapsule formation should be considered as a protective immunoinflammatory reaction against the metastastic nodule reflecting the host defence reaction creating a wall which stop tumor diffusion as re-

ported in the paper of Garancini et collegues[59].

2.3. Predictive of outcome related to surgery

Surgical margin >/10 mm in hepatic resection was a good prognostic factor in some papers. Miyazaki [70] demonstrated significant differences in the number of hepatic metastases (solitary of multiple) and the size of the tumor-free resection margin (<10 mm or >10 mm) for long and short term survivors. Thelen [32] reported that a positive resection margin should be considered a powerful determinant of poor outcome. Nomura [89] showed that the recurrence rate in the remnant liver was higher in patients with a surgical margin less than 5 mm.

The consensus seems to be that there is not apparent value to surgery if residual disease remains, whether it is involvement of resection margins, other distant metastases or peritoneal carcinosis.

The relationship between the extent of hepatic resection and prognosis has not yet been established. Isono [90] reported that micrometastases around the macroscopic tumor were found more frequently in hepatic metastases from gastric cancer than in those from colorectal ones, thus suggesting that wider surgical resection margins are required. A positive resection margin is also not an independent prognostic factor in colorectal liver metastases because of its strong relationship with the number of tumors resected. In approximately 70% of patients, recurrent disease developed after hepatic resection, most commonly in the liver. Recurrent tumors were more frequently distributed in both lobes than in the resected lobe, suggesting that liver recurrence is more probably derived from multiple metastatic foci from the primary disease than from intrahepatic tumor regrowth. As regard Nomura [89] underlined the role of intrahepatic micrometastases around liver as a cause of recurrence of the disease, pointing out that about 50% of patients with metastatic gastric cancer at the time of liver resection has already micrometastases. They stated that the presence of micrometastases was associated with poor results in term of survival after liver resection. This confirms how hepatic recurrence is associated with systemic spread through vessel or lymphatic circulation of the primary tumors. A generous surgical margin may not be essential for curative hepatic resection of liver metastases, even if in the study of Ambiru [11] a margin less of 10 mm is considered a poor prognostic factor for survival. Nevertheless a positive surgical margins should be avoided and the surgeon should strive to obtain an adequate margin, because this is the only prognostic factor on which the surgeon could have any influence over. According to the pattern of recurrence, relapse developed most commonly in the liver (70% range 63.6%-83.3%), indicating that the remaining liver should be a focus for relapse monitoring. The importance of the size of surgical-free margin was highlighted by other authors, whom showed how also a lower margin to < 5 mm can be regarded as negative factor both in terms of recurrence that of long-term survival [32,59,89]. Hired the need to maintain an adequate surgical-free margin from meta-

static lesion, emerged from the literature such as the size of the single metastatic lesion are not negligible in prognostic term. Kinoshita et al.[64] on a total of 256 patients enrolled in the multi-centre analysis identified the size ≥ 5 cm as an independent predictor of poor prognosis in term of overall survival.

The size of ≥ 5 cm as a poor prognostic factor was previously reported by Fujii *et al.* [87] and reconfirmed in some recent studies [67,78], but the data has not been confirmed by other authors [67,70,82,86].

In the more recent paper surgical margin has not been taken into account as a potential prognostic factor. Only the multi-centric study from Tiberio *et al.* [48] showed that R0 resection of the tumor bulk was a major prognostic factor and suggested that no effort must be spared to achieve it.

2.4. Timing of hepatic resection

The detection of a synchronous or metachronous metastases can be considered as a discriminating to perform surgery? At present we think was no. Until a few decades ago some paper reported synchronous disease as a significant poor prognostic factors. In fact they showed a significantly longer survival in patients with metachronous metastases than in those with synchronous disease. Ambiru *et al.* [11] reported a 3-year survival of 29% for metachronous versus 6% in synchronous lesions. Bines *et al.* [62] suggested a median survival of 8 months for synchronous disease and emphasized such as metachronous resection of isolated disease and multiple resections of recurrent isolated disease may have value in carefully selected patients. So some author suggest that resective treatment may be indicated only for the patient with metachronous isolated metastases [41,70]. A 3-year overall survival rate of 60% for metachronous versus 18% for synchronous disease was documented by Okano *et al.* [39], they also affirmed that a surgical approach for multiple and synchronous metastases may be of value as a part of combination therapy in carefully selected patients. Recently Schilberg et al. [76] against the trend of recent literature on the topic suggested a significant benefit for patient group with metachronous and solitary liver metastases, provided that R0 resection has been achieved. They reported a 5-year survival rate of 29% for metachronous versus 0% for synchronous metastases. In the last decade, many of the published studies seem to lead a changing in the surgical attitude for patients with synchronous metastases from gastric cancer (**Table 3 and 4**). Although most of the case studies were small series of patients and well selected and reported survival for synchronous lesions suggests that the en-bloc resection of the primary tumor with metastatic liver lesions leading to an improvement in survival. An analysis of the data reported in the recent literature showed that more than half 5-year survivors underwent a synchronous hepatectomy. In fact the recent meta-analysis of Markar *et al.* [55] that included 227 patients, 112 with metachronous and 115 with synchronous hepatic metastases demon-

strated no significant differences in 5-year overall survival for both groups. Other studies did not demonstrate any differences in term of survival among the groups; Cheon *et al.* [60] and Tsujimoto *et al.* [72] didn't observe a significant difference in survival between synchronous and metachronous metastases. Baek *et al.* [91] showed a 3-year overall survival for synchronous of 33% versus 38% for metachronous liver disease and they didn't find any significant factors that affected survival, probably for the limited number of patients examined. Recently the analysis of Qiu *et al.* [92] on 25 patients underwent synchronous hepatic resection reported a fifth of those alive at 5 years with an 1-,3- and 5-year overall survival of 96.0%, 70.4% and 29.4%, and recurrence–free survival rates of 56.0%, 22.3% and 11.1%. These data appear to suggest that survival for synchronous lesions, today, is not very different from that for metachronous metastases. In fact an analysis of the data reported in the recent literature showed that 27 of 55 5-year survivors underwent a synchronous hepatectomy. Also Takemura et al. [67] didn't highlights on a uniform group of patients for number (32 synchronous and 32 metachronous) any statistically significative difference in term of survival with a median of 34 months. Moreover in the Sakamoto's study [82] 3 of 5 patients who survived more than 3 years had synchronous solitary metastases and Ochiai [41] too reported three 5 years survivors with synchronous disease. In fact the studies of Qiu [92], Wang [83] and Tiberio [48] focused on the particular subset of patients with synchronous liver metastases and showed an overall survival similar to those regarding metachronous patients, offering the possibility of long-term survival. Thus, synchronous hepatectomy should not be a contraindication for hepatic resection. However it is clear that the concomitant resection of primary tumor with synchronous hepatectomy may lead to more high rate of post-operative morbidity. As regard Bines *et al.* [62] observed that synchronous resection carries a higher risk, but with no or small mortality occurred with 30 days after surgery as showed by other authors [55,92]. This may depend the concern regarding the use of aggressive liver surgery in conjunction with the treatment of gastric cancer under synchronous conditions.

Lymph node ratio may also a risk factor of prognoses among patients with synchronous GCLM who received combined surgical resection. A retrospective study found that patients with higher lymph node ratio had significantly shorter overall survival and recurrence-free survival than those with lower lymph node ratio [73]. In the multivariate analyses, higher lymph node ratio and multiple liver metastatic tumors were identified as the independent prognostic factors for both overall survival and recurrence-free survival. Elevated lymph node ratio was significantly associated with advanced pN stage, larger primary tumor size, the presence of microvascular invasion, and neoadjuvant chemotherapy. Therefore, lymph node ratio may be prognostic indicator for patients with gastric cancer liver metastasis treated by synchronous surgical resection.

However, data concerning long-term survivors demonstrate that, if we exclude bilobar

spread of metastases (H3), none of the reported predictive factors alone or in combination can deprive a patient of the possibility of long-term survival after hepatic resection, raising concern about the clinical value of prognostic factors emerging from small and superselected populations submitted to liver resection. Some data show that factors influencing survival were the extend of hepatic involvement and macroscopic peritoneal dissemination detected at surgical exploration [93,94]. When focusing on the subgroup of patients with unilobar or non disseminated bilobar metastases with negative peritoneal involvement ; the number of lesion, size of hepatic metastases and TNM stage of primary tumor were predictors of survival. All above mentioned studies strongly suggest that the main factor influencing long-term survival is the therapeutic approach to liver metastases, in particular when a surgical approach is performed. In some paper the presence of multiple poor prognostic factor displayed a cumulative effect. In the synchronous setting [48] gastric cancer T>2 and scattered bilobar metastases (H3) are negative prognostic factors: median and 5-year survival was respectively 23 months and 27% for the 10% of cases which did not display the two risk factors, while patients affected by T≥3 gastric cancer and H3 metastases (30% of cases) displayed a median survival of 6 months and did not survive more than 16 months. Accordingly, in the metachronous setting [94] the variable T4, N+ and G3 showed a negative prognostic role. Patients not presenting these variables (7%) had a 5-year survival rate of 40%, those affected by two or three negative prognostic factors (48%) had a median survival of 4±3 months.

2.5. Multi-centric studies

Based on the wind of change due to the results reported in such small single series published in literature, in the last years several multi-centric studies appeared (**Table 5 and 6**). One multi-centre retrospective analysis of 256 patients reported a promising median OS of 31.1 months [64]. Multivariable analysis identified serosal invasion of the primary gastric cancer, at least three liver metastases and liver tumour diameter of 5 cm or more as independent predictors of poor prognosis in terms of overall survival. These data has been confirmed in an Italian multi-centric study from Italian Research Group on Gastric Cancer [71]. Based on 105 patients a median overall survival of 14.6 has been reached, with an impact on survival related to T parameter and R0 resection: the Authors assumed that patients can obtain good survival performances even in presence of multiple scattered metastases in both lobes of the liver (H3), if all of them can be removed safely, pushes the tight limits in which the surgical indication is restricted in this particular field. This concept “enforces the idea that hepatic metastases may still be included in the concept of regional disease, which may benefit from regional surgery”. A propensity- matched analysis using a national database in the United Kingdom showed that the prognosis of patients who underwent both gastrectomy and hepatectomy was better than of those who received no surgery. A Japanese multi-institutional analysis from Komeda *et al.* [78] showed a median overall survival of 22.3 months and that size > 5 cm was a negative prog-

nostic factor for survival. Oki *et al.* [79] also from Japan reported a 3.3 years median overall survival in multi-centric group of 69 GCLM resected. Single tumors of less than 3 cm were the better candidates for surgical resection with a good outcome.

2.6. Review and meta-analysis

In the last years review articles follow each other with increasing frequency and almost parallel the number of research article but, fortunately, we also observe that the number of cases begins to rise. In fact, in 2010 Kerkar and *colleagues* [35] reviewed 436 patients collected from 19 surgical series published over a 20-year time-span, in 2014 Grimes *et al.* [95] reported on 438 cases and 17 papers; Romano *et colleagues* [96] on 434 and Fitzgerald *and colleagues* [97] collected 481 cases published in the period 1990 to 2013, but the last review and meta-analysis, published on line in the spring of 2016 [55], considered 991 patients who underwent liver resection for hepatic metastases from gastric cancer, recruited from 1990 to 2015. All the review concluded that in appropriately selected patients liver resection may offer a survival benefit. Where hepatectomy was undertaken, there was a significant morbidity rate but low mortality rate. The group of patients who may benefit most from hepatectomy are those with successfully treated primary disease and limited intrahepatic metastases. Those patients whose metastatic disease was synchronous, multiple or bilobar benefited less from hepatectomy, but otherwise should not be excluded from a potential treatment and than discussed on case by case analysis. In the last three years a number of meta-analysis has been published. Martella *et al*. [37] concluded that a statistically significant higher survival rate was found in the group of patients treated with local hepatic treatment of gastric cancer metastases compared to patients who underwent only palliation or systemic treatments and that curative surgery with complete resection of gastric cancer and hepatic metastases had a higher survival rate in comparison to palliative surgery of hepatic metastases or palliation. In 2016 a systematic review by Markar *et al.* [55] included 39 studies and 991 patients and concluded that is associated with 1-year, 3-year, and 5-year survivals of 68%, 31%, and 27%, respectively, and a median survival of 21 months and surgical resection was associated with better survival than other palliative treatments. Moreover number of metastases (solitary versus multiple), but not time of metastases (metachronous versus synchronous) was associated with an improved 5 years survival. Moreover Long *et colleagues* [36] concluded that compared with palliative treatment, resection was associated with significantly lower mortality at 1 year and 2 years and indicated that Asian cohorts showed higher median rates of overall survival at 1 year (73% vs 59%), 3 years (34% vs 25%), and 5 years (27% vs 17%). Moreover indicated good median overall survival rates of 68% at 1 year, 31% at 3 years, and 27% at 5 years. Median overall survival time was 21 months, which compares favorably with the 11.3 months reported for patients in a large randomized controlled trial who received combination chemotherapy of epirubicin, oxaliplatin, and capecitabine [20]. It also compares favorably with the 13.8 months reported for patients

who received both trastuzumab and chemotherapy involving the combination of cisplatin with capecitabine or fluorouracil. The last review published by Liao [98] in February 2017 suggested that hepatectomy is associated with substantially longer median overall survival than chemotherapy.

3. Repeat Resection for Recurring Metastases

The liver is the most common site for recurrence of metastases after resection for gastric cancer, with the recurrence rate of 57-87 %. It is rare that it is the sole site of recurrence and most patients receive non-curable palliative treatment. As in patients with colorectal liver metastases, a repeat hepatectomy may be considered in the absence of extrahepatic disease and if the patient has a good performance status and adequate hepatic reserve; however, repeat resection for GLM has rarely been reported. Recently, Takemura *et al.* [99] reported the result of an aggressive surgical approach for GLM including 14 repeat liver resections after 64 primary liver resections. In the report, the 5-year survival rate after repeat liver resections was 47 % which was comparable with those after the primary hepatectomy [67]. The mortality and morbidity rate were 0 and 29 %, respectively; however, the presence of severe adhesion around the liver hilum and the liver due to the previous primary lesion and liver resection concomitant with lymph node dissection makes repeat liver resection more challenging. The study demonstrated that a disease-free interval of >12 months after the initial hepatectomy predicts good patient survival after repeat liver resection. Otherwise the lack of data induce to be cautious regarding multiple repeated hepatectomy in this setting of patients

4. Conclusions

Till last years someone hold the view that liver metastatic gastric cancer represent a systemic disease and the “iceberg’s TIP” of a diffuse cancer, and surgery has no role in its treatment, because the results of liver resection are still disappointing. Worldwide the Societies for cancer treatment do not considered as a treatment for GCLM and excluded these patients from a surgical approach, with a passive attitude behaviour. Otherwise, with an analysis of series reported, mono-centric as well as multi-centric, we have found that more than 10% of patients survive more than 5 years after hepatectomy are tumor-free more than five years after liver resection, and the identification of favourable indicators of outcome could improve these results. The key of the success is to clearly identify the patients which could benefit of this treatment, in order to offer a chance of cure to the patients who have good prognostic factors and to avoid an over-treatment in case of absence of these factors. Moreover analysis of long term survival reported in literature shows that, if we exclude cases presenting a bilobar spread of metastases, none of the reported predictive factors, alone or in combination, can deprive a patient of the possibility of a long-term survival after hepatic resection. To date the results in the literature on the treatment of liver metastases from gastric cancer appear in parallel with

the results obtained for colorectal liver metastases, and the results in term of overall survival seems to be like the results obtained for colorectal liver metastases 15 years ago. So we have to expect that, as well as for colorectal metastases, with improvement of chemotherapy for gastric cancer associated with a multidisciplinary approach to these patients, an ulterior better prognosis could be achieved. The studies on the topic consist in small institutional series and with patients highly selected. A recruitment of a growing number of patients enrolled to hepatectomy, after a careful multidisciplinary assessment will clarify and confirm the therapeutic role of surgical resection for liver metastases from gastric cancer. In fact the promising results have been confirmed in a multi-centric setting with larger series. All the review articles and meta-analysis published in recent years, confirmed the superior value of surgery against palliative treatment. We believe that growing aggressive surgical treatment could provide a benefit and should be a part of multidisciplinary approach in patients with liver metastases from gastric cancer. A strong evidence that a "nihilistic" approach is no more justified for patients with GCLM emerged in the last few years. More centres shift their attitude from a passive approach to a more aggressive one, with a clear intention to treat and surgery, at least in referring centres, begins to be considered as one of the possible therapeutic options for these patients and has a role in the management of a well defined subset of metastases from gastric cancer. In fact In Gastric Cancer Treatment Japanese Guidelines nowadays has been reached the conclusion that hepatectomy could be considered in carefully selected cases of gastric cancer liver metastasis. In a recent of The EORTC and JCOG emerged that the strategy of preoperative chemotherapy followed by surgery should be further explored for resectable LMGC. Regarding unresectable LMGC, most of the sites perform chemotherapy only. However, with the future introduction of more effective chemotherapy, conversion strategies might occur. Thus, prospective data should be collected to build a basis for developing more effective treatment strategies for this population.

Compared to supportive treatment alone with a median survival of three to five months, the survival figures reported in literature indicate that liver resection can improve the prognosis of patients suffering from metastatic gastric cancer. This is true not only in Eastern experience, but also in Western countries, and in centres with skills and experience in liver surgery. A pragmatic multi-disciplinary approach, integrating neo-adjuvant and/or adjuvant chemotherapy, offers the possibility for further improvements in results.

5. Tables

Table 1: Literature analysis regarding hepatectomy for liver metastases from gastric cancer

Author year	N	Period	Resection Criteria	Resect-ability rate %	S/M	TG/ STG	Major/ Minor Liver surgery	Solitary	Multiple Uni/ BIlob	R1 %	Overall Survival % 1 3 5 ys	Long Term Survivor	Recurr-ence	morbidity/ mortality	Follow Up months
Ochiai 1994	21		No extrahepatic No carcinosis R0	Na	13/8	Na		14	7	0	19	19% (4)		na/0	na
Miyazaki 1997	21	1980-1995	No extrahepatic No carcinosis R0	na	11/10	na	5/16	7	14 11/3	Na	42 21 21	24% (5)	76.1%	na	na
Imamura 2001	17	1990-1997	No extrahepatic No carcinosis R0	na	7/10	na	6/11	8	9 4/5	18%	47 22 0	0	76%	na	Na
Ambiru 2001	40	1975-1999	No extrahepatic No carcinosis R0	na	18/22	19/21	21/19	19	21 5/16	0	70 28 18	15% (6)	75%	na/0	88
Fujii 2001	10	1979-1999	na	na	3/7	3/7	6/4	6	4 2/2	na	60 20 20	10% (1)	80%	na/0	10-240
Zacherl 2002	15	1980-1999	No extrahepatic No carcinosis R0	Na	10/5	9/6	3/12	8	7 2/5	33	35.7 14.3 0	0	90%	46%/6.7%	na
Saiura 2002	10	1981-1998	No extrahepatic ≤ 3 segments	15.6%	7/3	Na	6/4	5	5 4/1	40%	65 38 20	20% (2)	80%	na/30%	1-68
Okano 2002	19	1986-1999	No extrahepatic No carcinosis R0	17%	13/6	na	7/12	10	9 2/7	0	77 34 34	14% (3)	74%	na/0	13-148
Sakamoto 2003	22	1985-2001	No extrahepatic No carcinosis R0	8%	12/10	10/12	3/19	16	6 1/5	0	73 38 38	20% (5)	68%	na/5%	Na
Shirabe 2003	36	1979-2001	na	na	16/20	17/19	10/16	na	na	0	64 43 26	11% (4)	83.3%	na/0	NA
Roh 2005	11	1988-1996	No extrahepatic No carcinosis Solitary nodules R0	na	8/3	Na	2/9	11	0	0	73 42 27	18% (2)	80	na/0	Na
Koga 2007	42	1985-2005	No extrahepatic No carcinosis R0	17%	20/22	na	7/35	29	13	0	76 48 42	20% (8)	67%	na/5%	1-86
Sakamoto 2007	37	1990-2005	No extrahepatic R0 No carcinosis	12%	16/21	10/27	5/32	21	16 9/7	14%	60 27 11	6% (2)	81%	6%/0	Na
Thelen 2008	24	1988-2002	No carcinosis R0	na	15/9	na	8/16	13	11 5/6	25%	38 16 10	8% (2)	65%	17%/4%	1-67
Morise 2008	18	1989-2004	No extrahepatic R0 hepatic function	na	11/7	8/10	4/14	14	14	na	56.3 36.5 27	17% (3)	Na	na/0	2-200
Cheon 2008	22	1995-2005	No extrahepatic No carcinosis R0 hepatic function	7.5%	18/4	7/15	3/19	18	4 3/1	na	77 30.4 23	15% (3)	63.6%	na	1-106

Nomura 2009	17	1991-2005	No extrahepatic No carcinosis ≤ 5 lesions R0	na	9/8	Na	3/14	Na	Na	0	30.8	25% (4)	70.5%	na	1-117
Tiberio 2009	73	1990-2004	R0 no extrahepatic meta-chronous	15.1%	0/11	na	1/10	8	3	0	81 30 20	18.2% (2)	63%		4-86
Ueda 2009	72	1991-2005	na	16.6%	12/0	Na	4/8	9	3	1	57 43 43	20% (3)	na	na/0	na
Makino 2010	63	1997-2008	R0 no extrahepatic	21,00%	na	na	na	na	na	0	82 46 37	na	na	na	na
Choi 2010	14	1986-2007	No extrahepatic No carcinosis R0	Na	0/14	na	4/10	9	5 2/3	0	67 38..3	8% (1)	63%	na	na
Tsujmoto 2010	17	1980-2007	No extrahepatic No carcinosis Unilobar R0	na	9/8	Na	6/11	13	4	Na	31	30% (5)	70%	na/0	9-130
Dittmar 2011	15	1995-2009	R0 No extrahepatic	16,00%	9 6	na	2/8 5 RF	8	7 4/3		82 51 27	6% (1)	na	13%/0	01/01/59
Garancini 2012	21	1998-2007	No extrahepatic No carcinosis R0	31%	12/9	10/11	4/17	12	9 4/5	10%	68 31 19	14.2%(3)	66%	19%/0	6-90
Takemura 2012	64	1993-2011	R0 <3 mets	na	34/30	25/39	14/50	37	27	14%	84 50 37		67%	26%//0	3-174
Schildberg 2012	31	1972-2008	No extrahepatic unilobar	na	17/14	18/13	01/10/21	26	5	26%	6019 13	na	na	23%/6%	na
Yang 2012	13	2005-2008	No extrahepatic R0	na	13/0	8/05/12	06/07/12	6	7 1/6	38%	38 30 15	15%/(2)	85,00%	15%/0	2-39
Miki 2012	25	1995-2009	R0 No extrahepatic	Na	16/9	Na	Na	18	7	Na	73 43 36	Na	Na	Na	na
Aoyagu 2013	17	1995-2010	Na	22%	12/5	na	9/7	11	6 5/10	60%	75 35 17	17%(3)	Na	Na	na
Kostov 2013	28	1992-2006	R0 No extrahepatic	20%	24/4	Na	11/17	19	9 4/5	11%	68 38 28	18%(5)	83%	0/22%	12-122
Baek 2013	12	2003-2010	Solitary No extrahepatic	19%	9/3	Na	Na	11	1	8%	65 39 39	17%(2)	Na	0/0	1-85
Shinohara 2015	22	1995-2010	R0	46%	13/9	9/13	6/16	11	11 6/5	14%	82 33 26	14%(3)	Na	18%70	na
Ohkura 2015	13	1995-2014	Na	12%	9/4	Na	6/7	10	3	Na	88 30 30	30%(4)	69%	Na	1-69
Guner 2016	68	1998-2013	R0 No extrahepatic < 4 mets	Na	26/42	42/26	21/47	45	23 15/8	Na	79 41 30	Na	60%	28%/1.5%	4-189
Tatsubayas 2016	28	2004-2014	R0 No extrahepatic	Na	15713	Na	20/8	20	8	Na	91 56 32	Na	61%	0	26

S= Synchronous; M=Metachronous; TG= total gastrectomy; STG= subtotal gastrectomy;

Na: not available; mets = metastases

- number of patients resected on a total of patients with LMGC
- H3= Japanese Classification of gatric carcinoma: H1= metastases limited to one lobe; H2= few scattered metastases in both liver lobes; H3= numerous scattered metastases in both lobes

Table 2: Analysis of prognostic factors associated with survival in patients resected for LMGC

Author year	Num	age	Period	T	N	G	H	DIAM Metastases	TIMING S vs M	MARGIN	MST	Long Term Survivors	Recurrence	Recurrence free survival 1 3 5 yr	Pre-post CT	Follow Up months
Ochiai 1994	21			+	+	-	-	na	na	na	18	19% (4)	na	na	na	na
Miyazaki 1997	21	61(43-78)	1980-1995	-	-	-	+	na	-	na	11	24% (5)	76.1%	na	na	na
Imamura 2001	17	63(35-82)	1990-1997	-	+	+	-	na	+	+	16	0	76%	na	na	22.07.00
Ambiru 2001	40	63(37-75)	1975-1999	-	-	-	-	-	+	-	12	15% (6)	75%		na	88(4-296)
Fujii 2001	10	58(40-81)	1979-1999	-	-	-	-	+	+	na	16	10% (1)	80%	na	na	10-240
Zacherl 2002	15	62(37-81)	1980-1999	-	-	-	+	-	+	-	8.8	0	90%		na	na
Saiura 2002	10	55(41-70	1981-1998	-	-	-	-	-	-	na	25	20% (2)	80%	20	60,00%	29(1-68)
Okano 2002	19	69(52-79)	1986-1999	-	-	+	+	-	+	na	21	14% (3)	74%		55,00%	36(13-148)
Sakamoto 2003	22	63(52-89)	1985-2001	+	-	-	+	+	-	na	24	20% (5)	68%	na	60,00%	Na
Shirabe 2003	36	66(52-79)	1979-2001	-	Ly	-	+	-	-	-	NA	11% (4)	83.3%	na	na	NA
Roh 2005	11	52(43-79)	1988-1996	na	-	-	na	-	-	-	19	18% (2)	91,00%	na	na	Na
Koga 2007	42	64(44-89)	1985-2005	+	-	-	+	-	-	-	34	20% (8)	67%	na	33,00%	16(1-86)
Sakamoto 2007	37	64(39-76)	1990-2005	+	-	-	+	+	-	-	31	6% (2)	81%	na	18,00%	Na
Thelen 2008	24	64(41-84)	1988-2002	-	-	-	-	-	-	+	19	8% (2)	65%	33 10 10		9(1-67)
Morise 2008	18	64(51-76)	1989-2004	+	-	-	-	-	-	-	13	17% (3)	Na	na	na	117(2-200)
Cheon 2008	22	60(36-74)	1995-2005									15% (3)	63.6%	60 25 15	87,00%	15.5(1-106)
Nomura 2009	17	66(40-79)	1991-2005	-	-	-	-	-	-	+	18	25% (4)	70.5%	na	76,00%	20(1-117)
Tiberio 2009	73 (11)*		1990-2004	+	-	+	+		-	-	na	18.2%(2)	86,00%	na		15 (4-86)
Ueda 2009	72 (12)	67(25-85)	1991-2005	-	-	-	+	-	-	+	18	20%(3)	na	na	61,00%	na
Choi 2010	14	64(47-81)	1986-2007	-	-	-	-	-	-	-	NA	8% (1)	63%	na	na	na
Makino 2010	63 (13)	62(45-78	1997-2008	-	-	-	+	-	-	-	31	na	63,00%	na		na
Tsujmoto 2010	17	66.3	1980-2007	+	Ly	na	-	-	-	na	34	30% (5)	70%	na	na	29(9-130)
Dittmar 2011	15	57(25-82)	1995-2009	-	-	-	-	-	-	-	48	6% (1)	na	na	na	11(1-159)
Garancini 2012	21	64(44-89)	1998-2007									14.2%(3)	66%			6-90
Takemura 2012	64	65(32-89)	1993-2011	+	-	-	-	+	-	-	34	na	67%	42 27 27	69,00%	27 (3-174)
Schildberg 2012	31	65(35-84)	1972-2008	-	-	-	+	-	+	+	21	na	na	na	35,00%	na
Yang 2012	13	58(48-76)	2005-2008	-	-	-	+	-	na	-	12	15%(2)			85,00%	15(2-39)
Miki 2012	25	72(47-80)	1995-2009	+	-	-	+	-	-	Na	33	Na	Na	Na	35,00%	na
Aoyagu 2013	17	64(43-79)	1995-2010	-	+	-	+	-	-	na	Na	17%(3)	Na	Na	Na	na
Kostov 2013	28	68(51-81)	1992-2006	+	+	-	+	-	-	Na	Na	18%(5)	na	53 25 18	Na	48(12-122)
Baek 2013	12	61(51-74)	2003-2010	-	-	-	-	-	-	Na	31	17%(2)	Na	Na	40,00%	12(1-85)
Shinohara 2015	22	66(29-81)	1995-2010	+	-	+	+	-	-	Na	22	14%(3)	Na	42 26 26	72,00%	na
Ohkura 2015	13	64(47-71)	1995-2014	-	-	-	+	+	-	Na	Na	30%(4)	69,00%	Na	90,00%	22(1-69)
Guner 2016	68	61(30-75)	1998-2013	-	-	-	-	+	-	Na	24	0	60,00%	49 30 26	97,00%	24(4-189)
Tatsubayas 2016	28	72(39-86)	2004-2014	-	-	-	+	-	+	Na	49	7%(2)	61,00%	61 29 29	42,00%	26

S= Synchronous; M=Metachronous; TG= total gastrectomy; STG= subtotal gastrectomy;

Na: not available; mets = metastases

- number of patients resected on a total of patients with LMGC
- H3= Japanese Classification of gatric carcinoma: H1= metastases limited to one lobe; H2= few scattered metastases in both liver lobes; H3= numerous scattered metastases in both lobes

Table 3: Literature analysis regarding hepatectomy for liver metastases from gastric cancer in sinchronous setting

Author year	N	Period	Resection Criteria	Resectability rate %	TG/STG	Major/Minor Liver surgery	Solitary	Multiple Uni/BIlob	R1 %	Overall Survival % 1 3 5 ys	Long Term Survivor	Recurrence	morbidity/ mortality	Follow Up month
Wang 2012	30	2003-2008	Na	10	9/21	7/23	22	8	Na	43 17 17	16% (5)	na	12%/0	na
Qyu 2013	25	1998-2009	No extrahepatic R0	na	na	naW	16	9	Na	96 70 29	20% (5)	36%	/0	38(5-126)
Wang 2014	39	1996-2008	No extrahepatic R0	9%	5/34	Na	Na	Na 4/5	na	56 18 10	13%(4)	87%	7.7%/0	14
Tiberio 2015	52	1997-2011		na	18/35	0/52	na	na	0	60 17 11	12% (6)	92%	17/4	na
Zhoui 2016	21	1999-2010	No extrahepatic R0	2.7%	3/18	4/17	14	7	na	71 22 15	9% (2)	90%	48/0	15(3-114)

Table 4: Analysis of prognostic factors associated with survival in patients resected for LMGC in sinchronous setting

Author year	N	Period	Age	T	N	G	H	DIAM Metastases	TIMING S vs M	MARGIN	MST	Long Term Survivors	Recurrence	Recurrence free survival 1 3 5 yr	Pre-post CT	Follow Up months
Wang 2012	30	2003-2008	60(33-72)	-	-	-	+	na	Na	na	11	16% (5)	na	Na	30(100%)	
Qyu 2013	25	Na	1998-2009	-	-	-	+	+	-	na	38	20% (5)	36%(9)	56 22 11	14(56%)	38(5-126)
Wang 2014	39	64(38-81)	1996-2008	-	+	-	+	na	na	na	14	13%(4)	na	30 10 7	39(100%)	14
Tiberio 2015	52	68(	1997-2011	+	-	-	+	na	na	na	13	12% (6)	92%(49)	na	na	na
Zhou 2016	21	56(40-77)	1999-2010	-	+	-	+	na	na	na	na	9% (2)	90%(19)	na	21(100%)	15(3-114)

Table 5: Literature analysis regarding hepatectomy for liver metastases from gastric cancer: multicentric studies

Author year	N	Period	Resection Criteria	Resectability rate %	S/M	TG/ STG	Major/Minor Liver surgery	Solitary	Multiple Uni/BIlob	R1 %	Overall Survival % 1 3 5 ys	Long Term Survivor	Recurrence	morbidity/ mortality	Follow Up months
Komera 2014	24	2000-2012	No extrahepatic R0	Na	1/23	9/15	14/10	17	7	Na	78 40 40	17% (4)	66.7%	0	na
Kinoshita 2015	256	1990-2010	No extrahepatic R0	Na	106/150	99/157	73/183	168	84	10.2%	77 42 31	Na	75%(192)	10.9%/1.6%	65(1-261)
Markar 2016	78	1997-2012	Na	23%	71/7	Na	12/66	Na	Na	Na	60 42 36	Na	Na	10/	12
Oki 2016	69	2000-2010	Na	Na	28/41	Na	Na	28	41	10%	86 51 42	Na	Na	20/	25(1-142)
Tiberio 2016	105	1998-2013	Na	Na	74/31	Na	11/94	Na	Na	15%	58 20 13	12.4%(13)	82%	13%/1%	na

Table 6: Analysis of prognostic factors associated with survival in patients resected for LMGC in multicentric studies

Author year	N	Period	Age	T	N	G	H	DIAM Metastases	TIMING S vs M	MARGIN	MST	Long Term Survivors	Recurrence	Recurrence free survival 1 3 5 yr	Pre-post CT	Follow Up months
Komera 2014	24	2000-2012	Na	-	-	-	-	+	Na	Na	22.03.00	17%(4)	66.7%	Na	90,00%	na
Kinoshita 2015	256	1990-2010	Na	+	+	-	+	+	-	-	31.01.00	Na	75%(192)	44 32 30	17.6%	65(1-261)
Markar 2016	78	1997-2012	65	-	-	-	+	+	-	-	Na	Na	Na	Na	na	12
Oki 2016	69	2000-2010	Na	-	+	-	+	-	-	-	Na	Na	na	48 30 28	69,00%	25(1-142)
Tiberio 2016	105	1998-2013	68(57-74)	+	-	Na	-	Na	+	+	14.6%	12.4%(13)	82%	48 20 8	28,00%	na

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Chapter 4

Recent Research and Review Works in the Field of Gastric Cancer

Kai-Guang Zhang; Jun-Xia Tang; Jing Cui; Quan-Lin Guan*

Department of Surgery, Lan Zhou University, China

***Correspondence to: Quan-Lin Guan,** Department of Surgery, Lan Zhou University, China.*

Email: guanquanlin@163.com

Abstract

Gastric cancer is one of the leading causes of cancer-related death worldwide. Many patients have inoperable disease at diagnosis or have recurrent disease after resection with curative intent. Gastric cancer is separated anatomically into true gastric adenocarcinomas and gastro-oesophageal-junction adenocarcinomas, and histologically into diff use and intestinal types. Gastric cancer should be treated by teams of experts from diff erent disciplines. Surgery is the only curative treatment. For locally advanced disease, adjuvant or neoadjuvant therapy is usually implemented in combination with surgery. In metastatic disease, outcomes are poor, with median survival being around 1 year. Targeted therapies, such as trastuzumab, an antibody against HER2 (also known as ERBB2), and the VEGFR-2 antibody ramucirumab, have been introduced. In this review, we mainly resent an update of the treatment of gastric cancer.

1. Introduction

Gastric cancer is an important health problem, being the fourth most common cancer and the second leading cause of cancer death worldwide. More than 950,000 new diagnoses are made every year. An estimated 720,000 patients died from gastric cancer in 2012 [1]. Gastric cancer is separated anatomically into true gastric adenocarcinomas (non-cardia gastric cancers), of which there were 691,000 new cases in 2012, and gastro-oesophageal junction adenocarcinomas (cardia gastric cancers), of which there were 260,000 new cases in that year [2]. Despite a decline in incidence and mortality and despite important advances in the understanding of the epidemiology, pathology, molecular mechanisms, and therapeutic options and strategies, the burden remains high.

Gastric cancer is a main contributor to the global burden of disability-adjusted life-years from cancer in men and accounts for 20% of the total worldwide, following lung and liver cancers, which, respectively, account for 23% and 28% [3]. The burden of gastric cancer remains very high in Asia, Latin America, and central and eastern Europe, whereas in North America and most western European countries, it is no longer a common cancer [4]. Nevertheless, the decline in the incidence of gastric cancer has gradually lessened in some countries, particularly the USA. In other countries, such as France, mortality is predicted not to decrease further in the middle-aged population [4]. This slowing of change is probably explained by long-term low and stable prevalence of Helicobacter pylori infection in these countries [4]. By contrast, the incidence of gastro-oesophageal-junction adenocarcinomas is increasing sharply [5].

2. Surgical Treatment

Adequate surgical resection is the only curative therapeutic option for gastric cancer [6, 7]. Endoscopic resection might be suitable as an alternative to surgery for small well differentiated early-stage tumours [8,9]. Advances in technology and minimally invasive strategies have created new opportunities for surgery in gastric cancer. Minimally invasive procedures are associated with reduced surgical trauma and immunosuppression compared with conventional open surgery and, therefore, might improve quality of care as long as the principles of surgical oncology are respected.

The extent of surgery is determined by tumour stage, diameter, location, and histological type. Adequate surgery in the stomach is defined as complete resection of the primary cancer with tumour-free surgical margins of at least 4 cm and adequate lymphadenectomy. In practice, these requirements correspond to total gastrectomy for gastric cancers with signet-ring cells (linitis plastica), and those located in the upper third of the stomach or with atrophic gastritis. Cancer in the lower two-thirds of the stomach can often be treated with subtotal gastrectomy. Surgery in Japan and east Asia has traditionally been more extensive and aggressive than that in other developed countries. Although there is no worldwide consensus on the degree of lymphadenectomy, D2 lymphadenectomy (perigastric [D1] plus coeliac artery and its branches) is generally recommended if the associated postoperative morbidity and mortality rates are acceptably low-for instance, in high-volume hospitals with experienced surgeons [10]. This approach has contributed to improved cure rates in various registries and studies, from 30% to up to 55% in the past decade. Other reasons are stage migration because of improved methods for staging, increased use of adjuvant and neoadjuvant therapies, and centralisation of surgery, which has led to improvements in postoperative mortality [11]. At least 16 lymph nodes should be removed to enable adequate tumour staging and ensure optimum surgical resection.

Trans abdominal total gastrectomy is the standard surgical approach to treat patients with Siewert type II or III cancer of the gastro-oesophageal junction. The procedure is extend-

ed with a transhiatal resection of the distal oesophagus and lymphadenectomy of the lower mediastinum and the abdominal D2 nodal compartment. A thoracoabdominal approach in these patients can increase the risk of morbidity without improving survival and, therefore, is not usually recommended to treat cardia (type II) or subcardia (type III) gastric cancers [12].

Early gastric cancer is limited to the mucosa or submucosa (pathologically staged as T1 or lower), regardless of nodal status. Even in early gastric cancer, use of a multidisciplinary approach to determine the best therapeutic strategy (ie, endoscopic or surgical resection) is mandatory because lymph-node metastases occur in up to 20% of patients and correlate well with tumour penetration of the stomach wall and large tumour diameter [13,14]. Endoscopic versus surgical management of early gastric cancer has not been studied in randomised clinical trials, but surgical resection is viewed as the gold standard and is associated with 5-year recurrence-free survival of up to 98% [15]. For patients with early disease and suspected or histologically proven lymph-node metastasis, endoscopic resection should not be attempted. For mucosal gastric carcinoma, endoscopic resection is deemed sufficient in all European guidelines because the incidence of lymphnode metastatic disease is very low [9,14]. If the histopathological findings confirm a submucosal carcinoma after endoscopic resection, surgical resection that includes systematic lymphadenectomy has to be done, because lymph-node involvement is seen in up to 20% of these patients. Endoscopic resection of early gastric cancer should be done as a complete en-bloc resection to allow full histological assessment of the lateral and basal margins [9]. Patients who have endoscopic resection should be monitored frequently by endoscopic surveillance.

Most patients with locally advanced gastric cancer, which invades the muscularis propria and beyond (pathologically staged as T2 or higher), present with metastases in lymph nodes, distant organs, or both. Locally advanced gastric cancer might need en-bloc resection of involved structures. Prophylactic splenectomy is discouraged because it increases the risk of operative morbidity and mortality without any survival benefit, but might be necessary if the spleen or its hilar lymph nodes are affected [16]. Only patients without metastatic disease are potential candidates for surgical management with curative intent, although selected patients with peritoneal carcinomatosis or positive peritoneal cytology might benefit from aggressive surgery in expert centres [17]. Several randomised clinical trials and cohort studies have addressed the use of cytoreductive surgery with hyperthermic intraperitoneal chemotherapy for prevention and treatment of peritoneal carcinomatosis from gastric cancer. A systematic review and meta-analysis of 20 prospective randomised clinical trials involving 2145 patients suggested that cytoreductive surgery with hyperthermic intraperitoneal chemotherapy was associated with improved overall survival at 1, 2, and 3 years, but not at 5 years [18]. Most of the trials, however, did not fulfi l high-quality standards. With modern combination systemic chemotherapy regimens and biological agents, well designed randomised clinical trials with

robust methods are needed to confirm the potential benefits of this approach.

Over the past decade, minimally invasive surgery by laparoscopy has gained widespread acceptance in surgical oncology. The procedure seems to be feasible and safe and can represent an alternative to treat early and advanced gastric cancers in expert centres. A meta-analysis and systematic review 72 of studies with 3411 patients showed that laparoscopic distal gastrectomy compared with open surgery was associated with similar lymph-node dissection and long-term survival and with reduced intraoperative blood loss, postoperative complications, analgesic consumption, and length of hospital stay. Another meta-analysis 73 of data from 1819 patients in ten eligible studies showed similar overall and disease-free survival for laparoscopic and open gastrectomy in expert centres. Laparoscopic gastrectomy was also associated with similar lymph-node dissection and reduced intraoperative blood loss, postoperative complications, and length of hospital stay. However, because of potential study biases and notable heterogeneity between studies assessing short-term and long-term outcome measures in gastric cancer, data from well designed randomised clinical trials with robust methods should be awaited before laparoscopic gastrectomy is implemented in daily clinical practice.

3. Adjuvant and Neoadjuvant Therapies in Locally Advanced Disease

Adjuvant and neoadjuvant therapies are generally accepted to improve disease-free survival and overall survival in patients who have undergone adequate complete surgical resection (R0) of locally advanced gastric cancer by eradicating microscopic disease locoregionally and at a distance from the primary tumour. 5-year overall survival is increased by 10–15% with the addition of these treatments, but there is no global consensus about the optimum strategy. Perioperative chemotherapy additional to R0 is the most popular strategy in Europe, whereas in the USA it is postoperative chemoradiotherapy, and in Asia it is postoperative chemotherapy [6,7]. Adjuvant and neoadjuvant therapies are generally recommended for patients with T3, T4, or node-positive tumours.

Two European studies have shown improved outcomes with perioperative chemotherapy, including fluoropyrimidine-based and platinum-based chemotherapy, and with postoperative chemotherapy. In the MAGIC trial [19], treatment with three cycles of the epirubicin, cisplatin, and fluorouracil regimen before and after surgery was compared with surgery alone in patients with resectable stage II and III gastric cancers. In the chemotherapy group, 5-year overall survival was 36%, compared with 23% in the surgery alone group. A French study of perioperative fluorouracil and cisplatin showed similar results [20]. Fluorouracil is frequently replaced by capecitabine on the basis of findings from several studies, as discussed later in this Seminar. Subgroup analyses suggested the largest benefits are achieved in patients with gastro-oesophageal-junction tumours. Potential advantages of preoperative chemotherapy include the possibility of reducing tumour size and burden, controlling microscopic disease, and increas-

ing the likelihood of achieving an R0 resection.

The US 0116 trial randomised patients with T3, nodepositive, or both, gastric cancers to undergo surgery alone or with postoperative chemoradiation (bolus fluorouracil and leucovorin before, during, and after radiotherapy of up to 45 Gy in 1–8 Gy fractions) [21]. The potential advantage of the postoperative treatment is that patients are surgically and pathologically staged before it is started. The goal of postoperative radiation is to eradicate microscopic disease remaining in the surgical bed. By adding chemotherapy, malignant cells in the irradiated volume are radiosensitised and microscopic deposits outside are treated. Adjuvant chemoradiotherapy was associated with substantial reductions in overall and locoregional relapse. Subset analyses showed robust treatment benefits in all subgroups except patients with diff use histology [22], although this finding has been criticised, mainly because surgery was suboptimum (54% of patients underwent less than D1 dissection).

The ARTIST trial in South Korea was done to assess the efficacy of postoperative chemotherapy with capecitabine and cisplatin, with or without radiation to 45 Gy, in patients who underwent D2 lymph-node dissection [23]. Overall, the addition of radiotherapy to chemotherapy did not significantly extend disease-free survival or overall survival, but in patients with pathologically proven lymph-node metastasis, disease free survival was longer in those who received chemoradiation than in those who received chemotherapy alone (estimated 3-year disease-free survival 77.5% vs 72.3%, p=0.0365). The ARTIST-II trial is underway and is randomising patients with lymph-node-positive gastric cancer to receive postoperative chemotherapy or chemoradiation (NCT01761461). In the CRITICS study, being done in Europe, all patients with stage Ib–IVa nonmetastatic gastric cancer are being assigned to receive preoperative chemotherapy followed by at least a D1 resection, then random assignment to postoperative chemotherapy or chemoradiotherapy (NCT00407186).

Asian studies have shown traditionally larger benefits from an adjuvant chemotherapy than have those in developed countries. The Japanese ACTS-GC trial showed a survival benefit with the oral fl uoropyrimidine derivative S-1 after D2 resection [24], and the Korean CLASSIC trial [25] showed improved overall survival and disease-free survival with postoperative combined capecitabine and oxaliplatin. Moreover, although most other randomised studies showed no signifi cant benefit in overall survival with adjuvant chemotherapy, a large meta-analysis confirmed a 6% absolute survival benefi t with fluorouracil-based postoperative chemotherapy compared with surgery alone in all subgroups assessed [26].

Preoperative chemoradiotherapy is frequently used in patients with oesophageal and gastro-oesophageal junction tumours, although results from randomised trials of preoperative chemoradiotherapy in gastric cancer are not yet available. Preoperative chemoradiation has clear potential advantages. Delineation of the target for radiation is easier when the tumour is

still in place, and generally leads to smaller irradiated volumes and thus less acute and fewer late toxic effects than postoperative chemoradiation. Moreover, preoperative treatment leads to downstaging and downsizing, which increase the possibility of achieving an R0 resection. In theory, the tumour bed is better vascularised before than after surgery, which increases drug exposure and radio sensitivity. The Australian and European TOP GEAR phase 2/3 trial is being done to compare perioperative chemotherapy with preoperative chemoradiotherapy followed by postoperative chemotherapy (NCT01924819).

4. Chemotherapy Management in Gastric Cancer

The gastric cancer has a high recurrence rate after operation, especially in advanced stages. Patients with AGC whose performance status is adequate would normally be treated by systemic chemotherapy, aiming at improving cancer-related symptoms and extending life.

There is no international established standard chemotherapy regimen in current use, but several chemotherapeutic agents have been investigated for GC during the past several years, including platinum-based compounds (cisplatin and oxaliplatin), fluoropyrimidines (5-fluorouracil; capecitabine andS-1 in Asiatic countries), docetaxel (D), and the anthracycline asepirubicin (EPI) [27,28], but fluorourpyrimidine and platinum-based combininations are the most widely used in the world [27]. It remains controversial whether a triplet regimen is needed because the triplet regimen tend to bring out a higher toxicity profile and dissatisfactory of Overall Survival. A meta-analysis showed significant benefits from adding an anthracycline to a platinum and fluoropyrimidine doublet, and ECF (epirubicin plus cisplatin plus protracted infusion 5- fluorouracil) is among the most active and well-tolerated regimen [29].

A meta-analysis of gastric cancer trails has made a comparion between the triplet of DCF(docetaxel, cisplatin and 5-fluorouracil) and the triplet of ECF (epirubicin, cisplatin and 5-fluorouracil). The results suggest a similar activity of docetaxel and epirubicin. Evidence showed oxaliplatin was as effective as cisplatin and associated with lower toxicity and a slight survival benefit in patients who are older than 65 years. capecitabine, an oral fluoropyrimidine, was not inferior to fluorouracil in terms of progression-free and overall survival [30].

S-1 is a combination of tegafur, another orally active prodrug of 5-FU, combined with 5-chloro-2, 4-dihydropyrimidine, which prolongs the bioavailability of tegafur, and potassium oxonate, which reduces gastrointestinal. S-1 has shown benefit in advanced gastric cancer. In the multicentre, Phase III randomized trial, 1053 patients with advanced gastric or esophagogastric junction adenocarcinoma were randomized to either cisplatin plus S-1 or cisplatin plus 5-fluorouracil. The results showed no difference in median overall survival (8.6 months and 7.9 months, respectively), but cisplatin and S-1 were associated with a significantly better safety profile [31]. In Japan, the first-line regimen of chemotherapy for advanced gastric cancer is S-1 plus cisplatin. Whereas in the United States and Europe, S-1 remains unlicensed

because the Western FLAGS study showed no improvement in outcome with S-1 substituted for 5-FU in combination with cisplatin.

Irinotecan , a topoisomerase I inhibitor, was less toxic (improved tolerance) and can be an alternative when platinum-based therapy cannot be delivered. Several studies suggest that FOLFIRI (irinotecan with 5-FU) has activity as a first-line regimen [32]. Therefore irinotecan would be considered as reference regimens for second-line studies of novel agents.

5. Radiotherapy using in Gastric Cancer

Radiotherapy is used as important treatment for uncontrolled gastric bleeding and unresectable tumours. In these cases, radiotherapy did not improve survival, but locoregional control rates of 70% were reported. Importantly, due to the high incidence of locoregional failures after surgical treatment, radiotherapy has been regarded as an promising method for curative treatment of gastric cancer. Radiotherapy can be given intra-operatively, or preoperatively, or postoperatively (with or with out concurrent chemotherapy) with external beam radiotherapy.

There are trials suggesting that intra-operative radiotherapy can improve control of locoregional disease and lower locoregional recurrence rates. However, because most patients in countries without screening programmes present with advanced disease, overtreatment will happen in few patients.

Recently, a meta-analysis included 1581 patients, 507 in the intraoperative radiotherapy (IORT) group and 1011 in the control group. There was no significant difference in overall survival (OS) between the IORT group and control group (HR=0.91, 95% CI=0.73-1.13; P=0.38). And IORT showed favorable effects for patients with cancer in stage 2 and stage 3 and have the advantage of locoregional control [33]. Now a days, the radiotherapy is usually combined with chemotherapy to improve locoregional recurrence and offer a better life.

6. Targeted-Therapy Implement in Gastric Cancer

As in other solid tumours, the use of targeted agents that block these signalling pathways has recently emerged as a strategy for the treatment of advanced. GC. Up to now, just trastuzumab and ramucirumab have been shown to significantly improve survival in advanced GC patients.

Trastuzumab, a monoclonal antibody against HER-2 receptor, was the first targeted agent approved by FDA in GC patients. It has been considered as an effective targeted drug to improve overall survival when combined with systemic chemotherapy (cisplatin and a fluoropyrimidine) in advanced HER2-positive gastric cancer. In the Trastuzumab for Gastric Cancer (ToGA) trial, the addition of trastuzumab to chemotherapy significantly improved OS compared with chemotherapy alone in patients with HER2- positive AGC, achieving a median OS

of 13.8 months in the trastuzumab plus chemotherapy group. Tumour response rate, time to progression and duration of response were significantly improved in the experimental group compared with the CT alone group [34]. Recently, Primary and secondary resistance to trastuzumab has become a major problem and new strategies to overcome this resistance are needed. The other anti-EGFR mAbs, such as Cetuximab, matuzumab, Panitumumab , have not demonstrated improvements in survival among advanced GC patients effective “targeted therapies” in the treatment of AGC.

Ramucirumab, a completely humanized monoclonal antibody against VEGFR2, demonstrated either alone or in combination with paclitaxel (RAINBOW Trial) survival and disease control rate benefit as second-line regimen for non-Asian GC patients. In the phase 3 REGARD trial, 117 patients with metastatic gastric cancer progressive after first-line chemotherapy (a fluoropyrimidine and a platinum) were randomly assigned to receive ramucirumab or placebo plus best supportive care. ramucirumab group has showed a significantly better Overall surviva, with a similar survival benefit to that seen with conventional second-line chemotherapy . Ramucirumab combined with first-ling chemotherapy has become a useful option in second-line treatment in patients with good performance status scores and organ function [35].

With the understand of the tumor biology and cellular and molecular mechanisms responsible for malignant proliferation and tumor growth, new and more effective mocular targeted drugs needed to be found.

7. Conclusion

In a word, multidisciplinary synthetic therapy Should be used in treatment of gastric cancer. Besides, individual therapy is also important and should be payed more attention In gastric cancer treatment. Progress has been made in understanding the pathogenesis and the molecular biology of gastric cancer and in optimising the available treatment options and modalities. However, in the future, the focus should be on further unravelling the taxonomy of gastric cancer, fine-tuning treatment strategies, and developing new drugs for patients with advanced gastric cancer.

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Chapter 5

Postoperative Radiotherapy : Delineation of Target Volumes and Organs at Risk

H Ben Salah*; J Daoud[1]

[1]*Radiotherapy department, university Habib-Bourguiba hospital of Sfax Tunisia, Tunisia.*

****Correspondence to: H Ben Salah,** Radiotherapy department, university Habib-Bourguiba hospital of Sfax Tunisia, Tunisia.*

Email: bensalahh73@gmail.com

Abstract

It is imperative to review surgical and pathology reports and discuss with the surgeon, Prior to radiotherapy planning,to identify the areas considered to be the highest risk for recurrence. The type of operation needs to be noted. Radiotherapy planning CT scans should be done with a patient in the supine position with arms over head, from top of diaphragm (for stomach) or carina (for tumor of oesogastric junction or cardia) to the bottom of L4. Preoperative CT scans should be used to aid identification of preoperative tumor volume and nodal groups to be treated. Clinical target volume for adjuvant radiation therapy for gastric cancer depends on the location of the primary disease as well as the status of lymph node metastasis.

1. Introduction

Postoperative radiotherapy was integrated into the routine care of gastric cancer patients since the results of INT0116 study was published [1] This trial showed a survival and locoregional control benefit of adjuvant radiochemotherapy. Recommendations for postoperative radiation fields design have been published [2,3]. However they were largely based on two-dimensional radiotherapy planning using bony anatomic landmarks. Their implementation in three-dimensional (3D) conformal RT practice is challenging, which results in a large inter- and intraobserver variability in target volume delineation [4,5]. There are no consensus guidelines for target volume definition for postoperative radiotherapy in gastric cancer. This makes 3D computed tomography (CT)-based contouring of a clinical target volume (CTV) very difficult. Even with an anatomical delineation atlas, substantial variations in the CTV

delineation still occur between physiciens (**Figure 1**) [4,5].

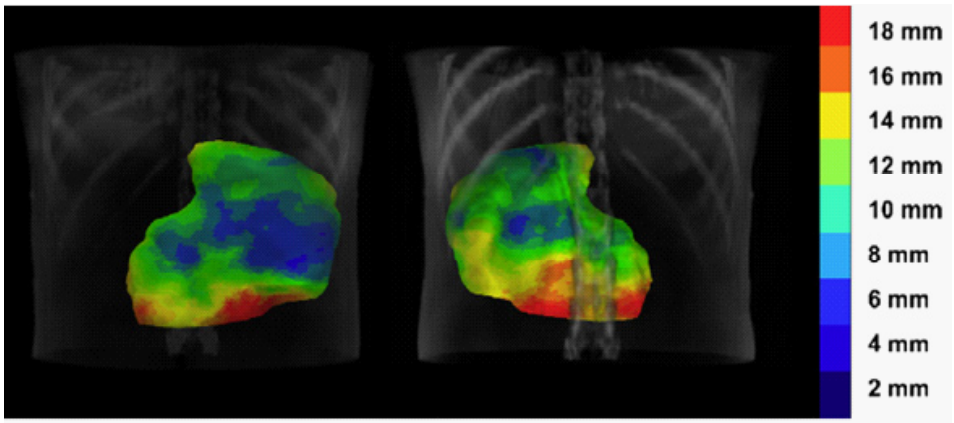


Figure 1: Anteroposterior and posterior views of a gastric cancer planning target volume. Red demonstrates large inter-observer variability and blue small variability [4].

2. Definition of Target Volumes

2.1. Cinical Target Volume (CTV)

The definition of target volumes is based on the characteristics of the tumor extension and the patterns of locoregional recurrence. Tumor extension includes invasion by contiguity, lymphatic extension and metastatic extension. Lymph node extension is very frequent conditioning the prognosis. Predicting lymph node involvement is difficult because of the submucosal or sub-serous lymphatics and abundant lymphatic chanels following the artery from the stomach. All lymph nodes schould be considered as a potential affected site [2,3,6]. In most studies of adjuvant radiotherapy, the target volume range is extremely diverse. Postoperative radiotherapy volume based on patterns of failure after radical surgery has been defined as the primary tumor bed, anastomosis site, duodenal stump, and regional lymph nodes [2,3]. If necessary, the remnant stomach in patients who underwent a subtotal gastrectomy has been often included [2,3].

Tumors confined to one of the proximal, middle or distal thirds of the stomach were analyzed with subdivision according to the position of the tumor on the circumference by Maruyama [7]. The incidence of metastases to any perigastric node station was highest when the tumor was located close to it, even though there was little variation in the metastatic pattern along the lesser curvature between tumors in the different thirds [7]. Station numbers 2 (left cardial) and 5 (suprapyloric, right gastric artery) were low-incidence stations for all locations of tumors (**Table 1**). The position of the tumor on the stomach circumference had a similar impact, as shown for distal cancers (**Table 1**). Similarly tumors along the lesser curvature or on the anterior or posterior walls had splenic hilar node metastases in up to 6% [7].

Table 1: Incidence of node metastases from cancer s in various part of the stomach [7].

Lymph Node station Number	A N=339	M N=318	C N=150	A tumors on the			
				Lesser Curvature	Anterior Wall	Greater Curvature	Posterior Wal
1	7	16	31	11	0	3	7
2	0	1	13	(0-1)	(0-1)	(0-1)	(0-1)
3	38	40	39	42	27	32	33
4	35	31	11	25	44	49	26
5	12	3	2	15	3	7	0
6	49	15	3	39	32	62	30
7	23	22	19	25	21	23	11
8	25	11	7	34	9	25	15
9	13	8	13	16	3	12	7
10	0	2	10	(0-1)	(0-1)	(0-1)	(0-1)
11	4	4	12	7	0	1	0
12	8	2	1	12	3	6	0
13,14,15,16	(0-5)	(0-5)	(0-5)	(0-5)	(0-5)	(0-5)	(0-5)

A,M,C: distal,middle and proximal thirds of the stomach, respectively.

The inclusion of node stations in the CTV is based on these findings.

The 2002 Gastric Surgical Adjuvant Radiotherapy Consensus Report discussed gastric anatomy and pathways of tumor spread, described patterns of failure, and detailed treatment planning guidelines for adjuvant 2 D radiotherapy. This report mandated coverage of the gastric tumor bed, the anastomosis or stumps, and the regional lymphatics. Detailed recommendations was made in this report [2]. Administration of barium at the time of simulation was recommanded to identify the anastomosis and gastric stump. Review of preoperative computed tomography (CT) scans was mandatory to identify the preoperative location of the tumor and regional lymphatics, and placement of radiopaque clips at the time of surgical resection (**figure 2,3 and 4**) [2].

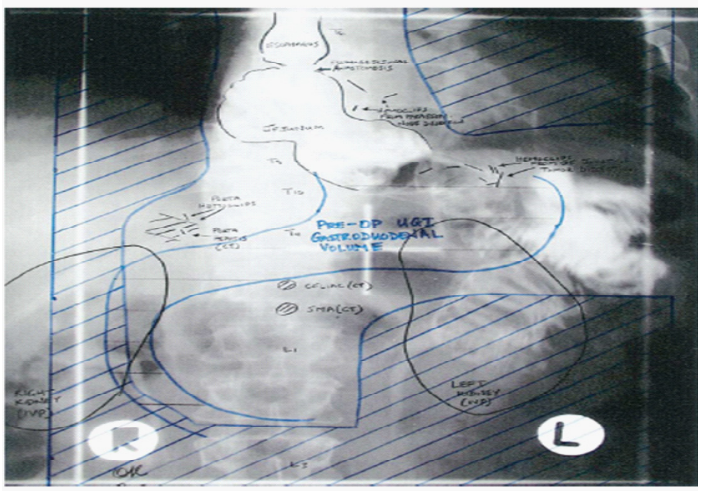


Figure 2: Simulation film for T4 (diaphragm invasion) cardial tumor with 4of 15 nodes involved with tumor. Preoperative CT identifies tumor bed. The anastomotic line is easily identified on barium swallow and by staple line. Regional lymph node location is reconstructed from CT scan.

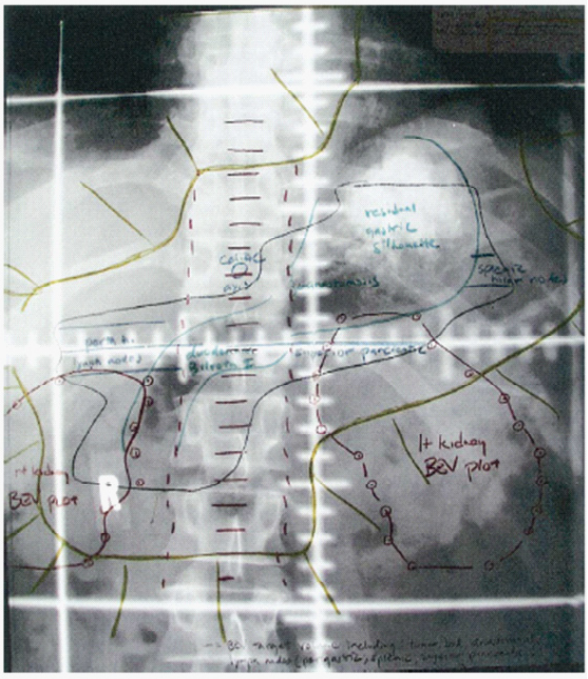


Figure 3: Simulation film for a T3 antral primary two of six regional nodes. The Billroth I anastomosis staple line is identified that connect the gastric remnant with the duodenum. Beam's-eyes-view reconstruction identifies the original tumor bed, the anastomosis and regional nodes (perigastric, retropancreatic, porta hepatis, celiac and pancreaticoduodenal nodes that are in an aberrant location because of the Billroth I procedure) at risk.Though splenic nodes are at relatively low risk, their proximity to residual perigastric nodes makes inclusion of these nodes not an issue of increased radiotherapy toxicity [2].

Tepper and Gunderson published a report entitled Radiation Treatment Parameters in the Adjuvant Postoperative Therapy of Gastric Cancer. This report provided detailed guidelines on appropriate radiation treatment volumes stratified by primary tumor site within the stomach (oesogastric jonction, proximal, middle and distal staomach) and by tumor (T) and node (N) stage[3].

Delineation of target volumes for tridimensional conformal radiotherapy requires intravenous contrast-enhanced planning CT with a 3-5mm slice thickness. This CT simulation is performed in the supine position with arms overhead, from top of diaphragm (for stomach) or carina (for tumor of oesogastric junction or cardia) to the bottom of L4. Patients should be fasted for 2–3 hours. Intravenous contrast is preferred to demonstrate blood vessels and guide clinical target volume (CTV) delineation, particularly for lymph nodes.The already defined lead marks are taped to the skin.

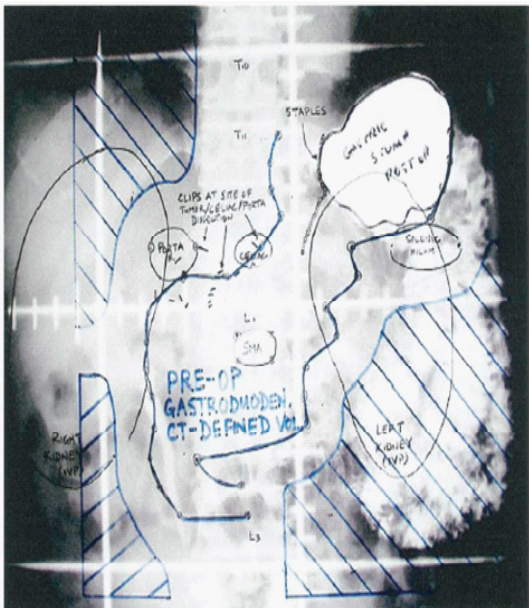


Figure 4: Simulation film for T3 antral tumor with two of five peritumoral lymph nodes metastatically involved. Simulation film shows areas at risk of locoregional relapse. Preoperative tumor bed is identified by preoperative CT scan: staple lines help locate duodenal stump and area of gastric transection. Regional lymphatics are identified from CT scan. Splenic nodes are included with tolerable kidney volumes [2].

The CTV is defined in the best conditions from the preoperative dosimetric scan and an image adjustment performed with the postoperative CT scan (**figure 5,6**) [8].

In the absence of a preoperative dosimetric scanner, a fusion of the diagnostic scanner and the scanner in the treatment position is performed [8].

Whatever the seat of gastric cancer - apart from cardiac tumors - all the stomach is included in CTV as well as anastomoses and lymph nodes.

These structures are contoured on each CT slice for delineation of the clinical target volume (CTV) [8].

Two CTV are described. A first CTV which includes the oes-jejunal or gastro-jejunal anastomosis, the gastric stump, the gastric bed reconstructed from a preoperative scan and lymph node areas. Ideally, clips are set up by the surgeon to delimit the operating bed, the initial site of the tumor and sites at risk of relapse (R2 residue, fixed lymph node groups). The second CTV includes sites at risk of relapse [8,9].

For most gastric cancers, L3 represents the lower limit of CTV. This lower limit allows the inclusion of nodes 5, 6, 7, 8, 9 and 12 [8,9].

Mineur and al detailed nodal sites included in the volume CTV 1 as follows in the **table 2**

Table 2 : nodal sites included in the volume CTV 1 according to Mineur [8].

Tumor site	Nodal sites included in CTV1
Cardia	1,2,3,7,8,9
Fundus	1,2,3,4,5,6,7,8,9,10,11
The lesser curvature or the greater curvature	1,2,3,4,5,6,7,8,9,10,11
The gastric antrum	1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16

Hennequin detailed nodal sites included in the volume CTV 1 as follows in the table 3

Table 3: nodal sites included in the volume CTV 1 according to Hennequin [9].

Tumor site	Nodal sites included in CTV1
Gastric body or fundus	1,2,3,4,5,6,7,8,9,10,11,12
Oesogastric junction	1,2,3,4,7,8,9,10,11
The gastric antrum	1,2,3,4,5,6,7,8,9

2.2. Planning target volume (PTV)

The margin defining PTV is 2 cm [8,9,10]. This margin corresponds to the positioning errors and to the movements of organs. The median displacements of the critical organs are 6 mm in a cranio-caudal axis and 2 mm in the other directions. Wysocka et al. Recommended a caudal-caudal margin of 1 cm and a margin of 5 mm in the other axes with an individual approach for patients with high respiratory amplitude [11]. Caudry et al. Have proposed to reduce this margin to 10 mm under the condition of rigorous control of patient placement (restraint, laser, supine position, portal imaging) [12].

3. Delineation of Target Volumes

As radiation treatment fields become increasingly conformal in an attempt to limit dose to normal critical structures, it becomes increasingly important to accurately identify treatment volumes on CT-based planning images. Based on studies evaluating the patterns of relapse after surgical resection, general guidelines have been proposed to aid in definition of the clinical target volume for adjuvant radiation treatment fields based on location, T stage of the primary tumor, and N-stage. For node positive disease, wide coverage of the tumor bed, residual stomach, resection margins, and nodal drainage regions have been generally recommended. Mineur has published illustrative figures of the delineation of CTV (**figure 5,6**)[8].

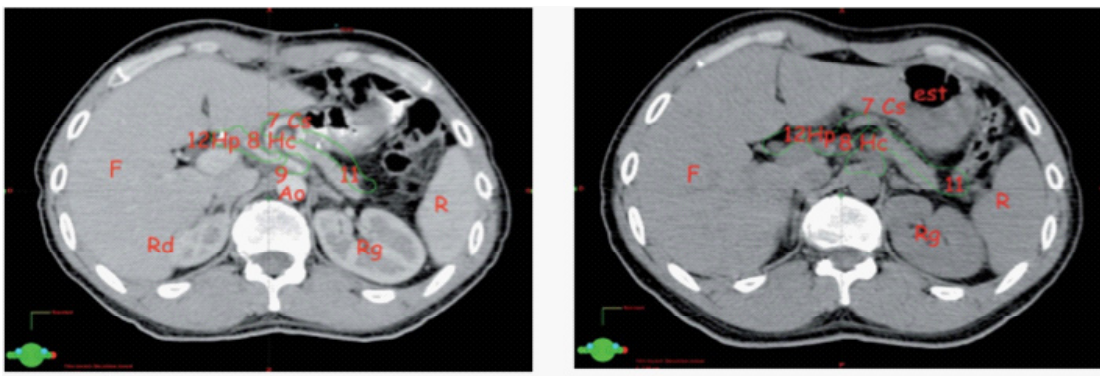


Figure 5: CT delimitation of the subdiaphragmatic lymph node territories involved in stomach cancers on preoperative and postoperative CT. 7: left gastric artery (Cs), 8: common hepatic artery (Hc); 9: celiac trunk; 11: splenic artery lymph nodes; 12: hepatic artery (Hp). AO: descending aorta; Rd: right kidney; Rg: left kidney; F: liver [8].

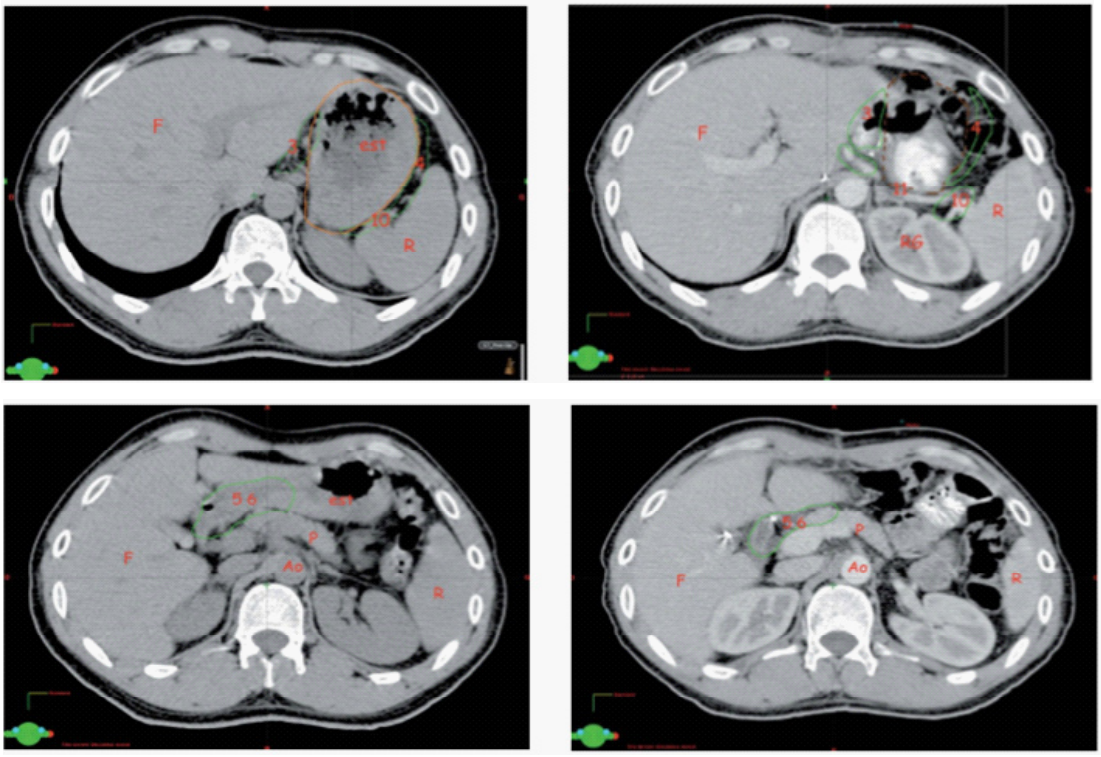


Figure 6: repositionning of the stomach on the postoperative CT after adjustment (brown dotted line) and identification of lymph node territories, view with representation of areas 3,4 (small and large curvature, 7 (left gastric artery) 10,11 (splenic artery and hilum) [8]

By inclusion of the preoperative tumor bed and resection margin, more often than not the preoperative perigastric lymph node drainage basin is naturally included within the target volume [13]. A gastric lymph node (LN) contouring atlas is meant to supplement the previously established guidelines for definition of CTV in the adjuvant treatment of gastric cancer [13]. This report serves as a template for the delineation of gastric lymph node stations to aid in the definition of elective clinical target volumes to be used in conformal treatment planning [13].

Although generally the radiographic definitions of gastric LN stations described for intact gastris anatomy can be applied in the postoperative setting (**figure 7**), due to the potential for differences in postsurgical anatomy it is important to discuss radiographic identification of gastric LN stations in the setting of the most common oncologic surgeries employed for resection of gastric cancers (**figure 8,9,10**)

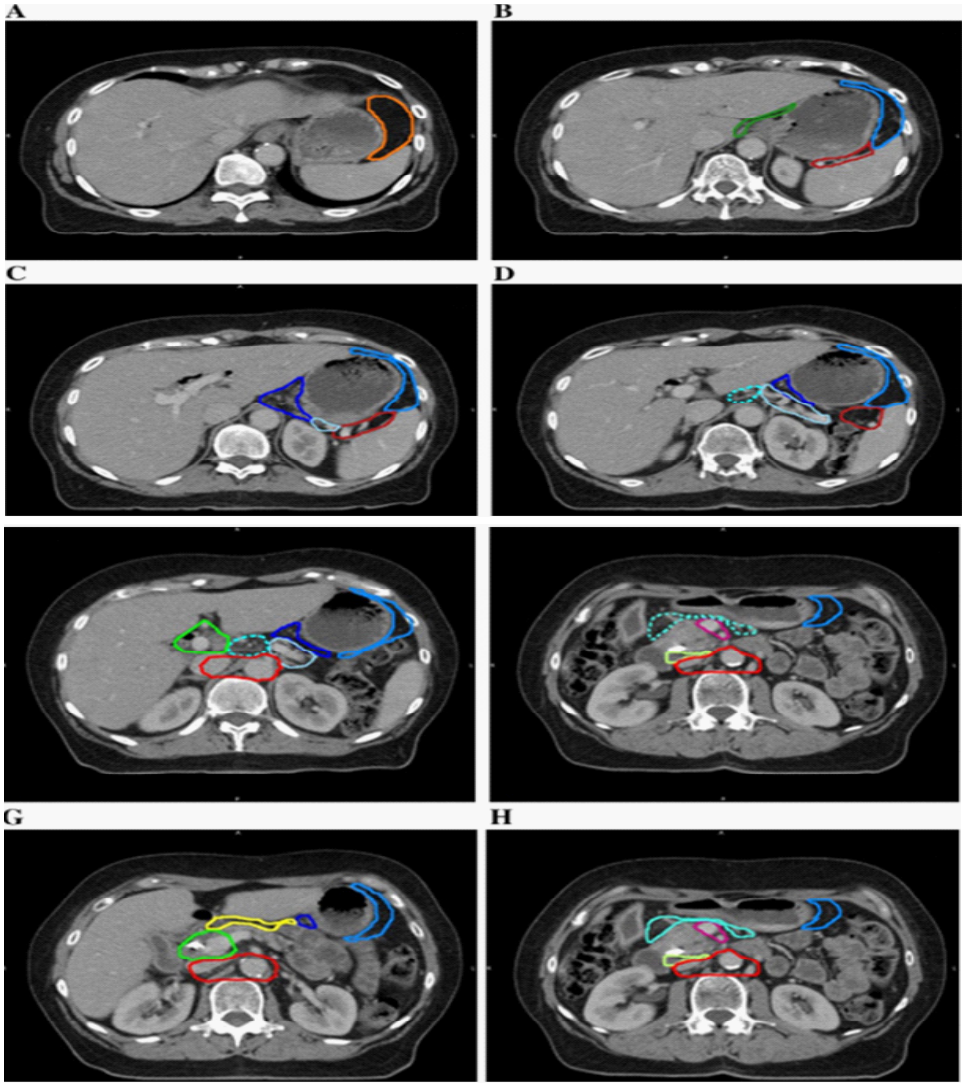
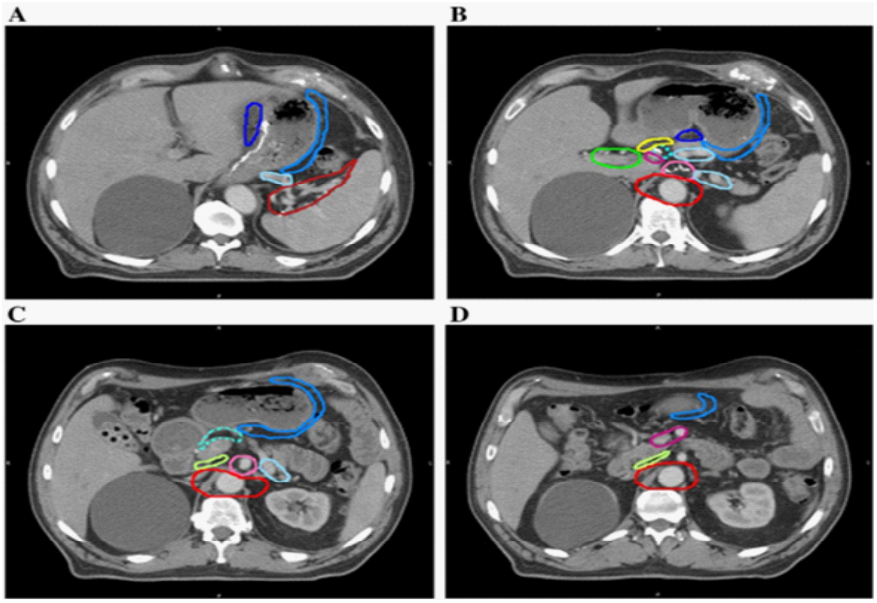


Figure 7: intact gastric anatomy. (A) left paracardial (orange); (B) greater curvature (blue), splenic hilum (brown), right paracardial (forest green); (C) greater curvature (blue), lesser curvature (dark blue), splenic hilum (brown); (D) greater curvature (blue), lesser curvature (dark blue), splenic (sky blue), splenic hilum (brown), left gastric (aquamarine, dashed); (E) greater curvature (blue), lesser curvature (dark blue), splenic (sky blue), left gastric (aquamarine, dashed), paraortic (red), hepatoduodenal (bright green); (F) greater curvature (blue), lesser curvature (dark blue), splenic (sky blue), paraortic (red), hepatoduodenal (bright green), common hepatic (dark purple), celiac (pink); (G) greater curvature (blue),), lesser curvature (dark blue), paraortic (red), hepatoduodenal (bright green), suprapyloric (yellow); (H) greater curvature (blue),), paraortic (red), pancreatic (lime green), superior mesenteric (violet), infrapyloric (green dashed).



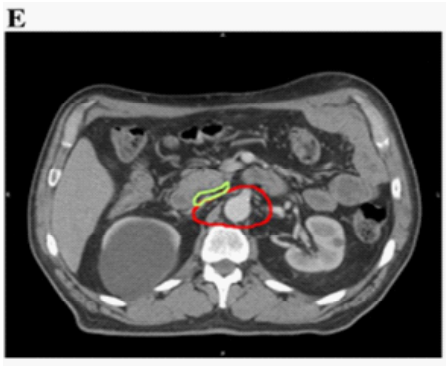


Figure 8: Ivor-Lewis eosophagogastrectomy. (A) Greater curvature (blue), lesser curvature (dark blue), splenic hilum (brown), splenic (sky blue); (B) greater curvature (blue), lesser curvature (dark blue), splenic (sky blue), hepatoduodenal (bright green), suprapyloric (yellow), celiac (salmon pink), common hepatic (dark purple), left gastric (aquamarine, dashed), paraortic (red); (C) greater curvature (blue), pancreatic (lime green), celiac (salmon pink), splenic (sky blue), paraortic (red), infrapyloric (green dashed); (D) greater curvature (blue), superior mesenteric (violet), pancreatic (lime green), paraortic (red); (E),), pancreatic (lime green), paraortic (red).

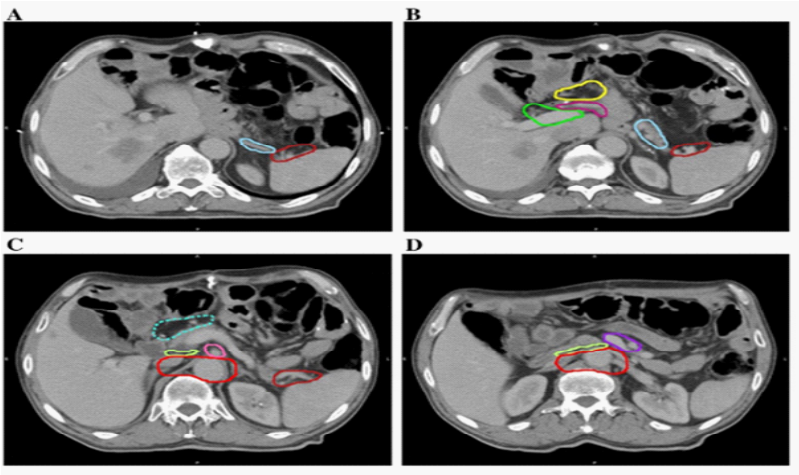


Figure 9: Total gastrectomy with roux-en-Y esophagojejunostomy. (A) splenic hilum (brown), splenic (sky blue); (B) splenic hilum (brown), splenic (sky blue), hepatoduodenal (spring green), common hepatic (dark purple), suprapyloric (yellow); (C) splenic hilum (brown), paraortic (red), celiac (salmon pink), pancreatic (lime green), infrapyloric (green dashed); (D) paraortic (red), pancreatic (lime green), superior mesenteric (violet).

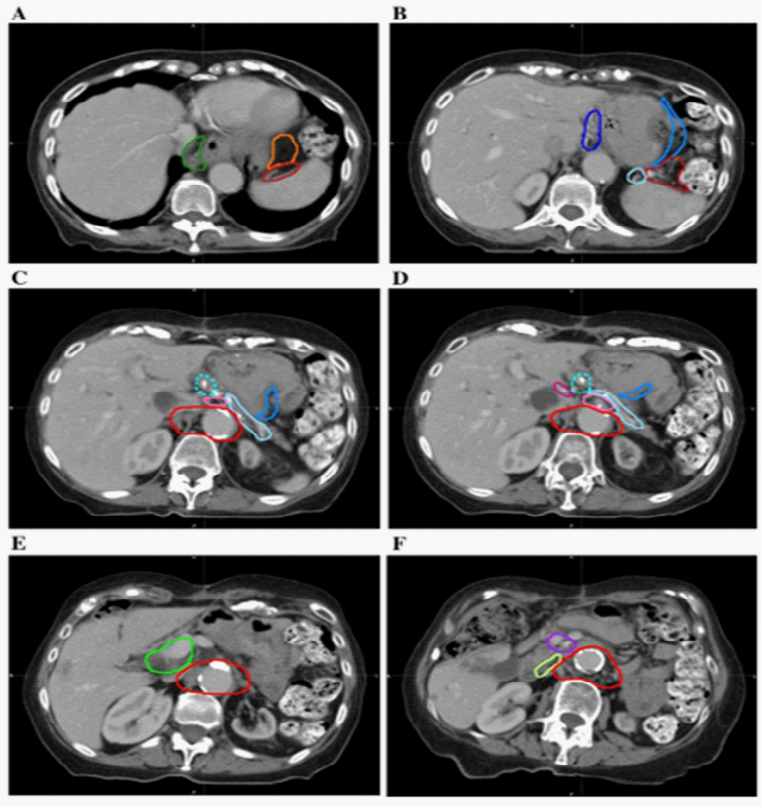


Figure 10: Subtotal gastrectomy. (A) R paracardial (forest green), L paracardial (orange), splenic hilum (brown); (B) lesser curvature (dark blue), greater curvature (blue), splenic (sky blue), splenic hilum (brown), (C) greater curvature (blue), splenic (sky blue), paraortic (red), left gastric (aquamarine, dashed), celiac (salmon pink); (D) greater curvature (blue), splenic (sky blue), paraortic (red), left gastric (aquamarine, dashed), celiac (salmon pink), common hepatic (dark purple); (E) hepatoduodenal (spring green), paraortic (red); (F) pancreatic (lime green), paraortic (red), superior mesenteric (violet).

4. Organes at Risk

Organs at risk are kidneys, liver, heart, lung, and spinal cord. Their delineations is easy.

5. References

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Chapter 6

Tumor-Associated Neutrophils (TANs) in Gastric Carcinomas: Clinicopathological and Prognostic Implications

Caruso RA[1]*; Rigoli L[1]

[1]Department of Human Pathology in Adult and Developmental Age "G. Barresi", University of Messina, Messina, Italy.

**Correspondence to: Caruso RA, Department of Human Pathology in Adult and Developmental Age "G. Barresi", University of Messina, Messina, Italy.*

Email:rocaruso@unime.it

1. Introduction

Gastric cancer, the fifth most common cancer worldwide, and the third leading cause of cancer-specific mortality, has very poor prognosis, with a 5-year survival less than 30% [1-2]. The TNM staging remains the cornerstone in clinical oncology to stratify prognosis and establish therapy for patients with neoplasm [3]. Gastric carcinoma is a heterogeneous neoplasm with respect to anatomic location, epidemiology, genetics, histopathology, and biologic behavior, and, consequently, it has been subjected to many different classifications. With respect to anatomic location, gastric carcinomas may be distinguished as proximal (also known as cardia) and distal (also known as noncardia). This classification correlates with distinct epidemiological risk factors. Obesity, hiatal hernia and reflux gastroesophagitis all are associated with cardia carcinoma, whereas H pylori infection is responsible for 77% of distal carcinoma [4-6]. From a histopathological viewpoint, routine classifications include those proposed by Laurèn [7], WHO [8], and Goseki [9]. The Laurèn classification [7] recognizes two main histological types: intestinal and diffuse, which show correlations with distinct clinical and epidemiological features. Intestinal type adenocarcinoma is mainly found in high risk areas of gastric cancer and is associated with the global decrease in incidence of this tumor. Histologically, intestinal type adenocarcinoma consists of tumor cells showing glandular differentiation with tubular, papillary or tubulo-papillary growth pattern. In diffuse type gastric carcinoma, tumor cells show abnormal loss of glandular differentiation and invade the stroma singly or in small groups. The WHO classification [8] is based on the predominant morphological component of the tumor (usually >50%) and identifies five types of gastric carcinoma: papillary, tubular, mu-

cinous, poorly cohesive (including signet-ring cells and other variants) and mixed carcinomas. Goseki classification [9] combines two tumor features, tubular differentiation and amount of intracytoplasmic mucus, in the following four groups: Group I (good tubular differentiation, poor mucus amount in cytoplasm), Group II (good tubular differentiation, rich mucus amount in cytoplasm), Group III (poor tubular differentiation, poor mucus amount in cytoplasm), Group IV (poor tubular differentiation, rich mucus amount in cytoplasm). Recently, The Cancer Genome Atlas (TCGA) research network suggested a molecular classification of gastric carcinoma in four subtypes based on the presence of Epstein-Barr virus (8.8%), microsatellite instability (21.6%), genomic stability(19.6%) and chromosomal instability(49.6%) [10]. This biomolecular classification offers several advantages, showing particular correlations with anatomic location and/or tumor histologic types. Tumors with chromosomal instability occur more frequently at the gastroesophageal junction and in the cardia, whereas Epstein-Barr positive tumors arise more frequently in the fundus and body. Genomic stable tumors show diffuse histology and are characterized by CDH1 and RHOA mutations. Epstein-Barr virus tumors display PIK3CA mutation as well as JAK2 and PD-L1/2 overexpression. Tumors with chromosomal instability exhibit intestinal morphology, marked aneuploidy, TP53 mutation and focal amplification of receptor tyrosine kinases. Microsatellite unstable tumors show elevated mutation rates, including mutations of genes encoding targetable oncogenic signaling proteins. However, from a prognostic viewpoint none of these 4 subgroups of gastric cancers showed any significant survival differences. Although H pylori is responsible for 77% of distal carcinoma, H pylori status was not evidenced in this molecular classification [11-12]. Therefore, further studies are needed to demonstrate that TCGA gastric cancer classification may have practical implications for improving both therapy and survival in these patients.

Gastric carcinoma heterogeneity is reiterated by the strong variability in the host inflammatory reaction. The WHO classification [8] describes four stromal reactions (desmoplasia/scirrhous reaction, lymphocytic infiltration, stromal eosinophilia, and a granulomatous response), neglecting the role of tumor associated neutrophils (TANs) in gastric carcinomas. Traditionally, neutrophils were considered cell protagonists of the acute phase of inflammation, where they play an important role in the defense against microbial invasion. Recent studies have widened this view showing new functions of neutrophils including the orchestration of innate and adaptive immune reactions [13-15]. In recent decades, increasing attention has been paid to the role of neutrophils in tumor-host reaction, but conflicting conclusions on the prognostic impact of TANs have been reported in literature.

In this work, we summarize the current state on the clinicopathological and prognostic implications of TANs to elucidate this problem. Our experience with TANs in gastric carcinomas is also reported and discussed according to recent data from literature.

2. Neutrophil-To-Lymphocyte Ratio(NLR)

Blood counts, such as the NLR, are being used for diagnostic and prognostic aims in patients with cancer [16-22]. Indeed, NLR has also been used for early detection and as a prognostic marker in gastric cancer [23-25], early diagnosis of ovarian cancer [26-27], and prognosis and survival prediction in colon cancer [28] and hepatocellular carcinoma [29]. Recently, NLRs have also been used in the differential diagnosis between primary breast carcinoma and benign proliferative breast disease [30]. In most studies, a high NLR is associated with adverse overall survival in many human tumors. However, NLR data must be considered with caution, as they are nonspecific parameters, which may be influenced by concurrent conditions such as infections, inflammation, and medications [31]. Many studies did not explicitly check for such concurrent conditions, and this may lead to erroneous interpretations [31]. Furthermore, there are few works regarding NLR values in patients with a low/high neutrophil count in the tumor.

3. N1 and N2 – Polarization or Hyperactivation

Experimental studies suggest that TANs show a bipolar pattern of activation (N1/N2) similar to that observed in macrophages (M1/M2) and T-cell (Th1/Th2) polarization [32-33]. N1 neutrophils exert antitumor activities through tumor cytotoxicity, whereas N2 neutrophils favor tumor growth, invasion and metastasis, e.g. through proteolysis of extracellular matrix components, promotion of angiogenesis and mediation of immunosuppression [34-38]. However, N1/N2 neutrophils have only been shown in murine tumor models and must be confirmed in human tumors [39]. It is also possible that the N1/N2 phenotype reflects only a functional state of neutrophil activation [39-40]. For example, neutrophils isolated from early tumors are more cytotoxic toward tumor cells and release higher levels of NO and H_2O_2, whereas in advanced tumors, neutrophils display low cytotoxic activity and acquire a protumor phenotype [41]. These data suggest that tumor stage plays an important role in modeling neutrophil phenotype and function.Therefore, further studies are needed to clarify whether the different functions of TANs can be attributed to distinct subpopulations, or rather to different grades of neutrophil activation in human tumors.

4. Distribution of TANs and Neutrophil Recruitment in the Tumor Stroma

Distribution of TANs is multifaceted. TANs may be found at the invasive front of tumor (peritumoral location) (**Figure 1a**) or in the center of tumor (**Figure 1b**) [42-46]. Intratumoral TAN distribution shows heterogeneity, being found as a single massive infiltrate in the tumor stroma or as a series of multifocal aggregates scattered throughout the tumor stroma. In some cases numerous neutrophils may be found within the tumor epithelium (**Figure 2**) [47]. It has been pointed out that peritumoral TANs are mainly found at the early stage of tumor development, while intratumoral TANs are seen at later stages [48].

4.1 TANs and tumor necrosis

Mechanisms responsible for neutrophil infiltration in the tumors may be manifold. It is a common experience of pathologists to observe neutrophils in the tumor stroma using light microscopy, and, to date, this phenomenon is interpreted as secondary to tumor necrosis. Consequently, areas of tumor necrosis are not taken into consideration during a TAN count. However, the role of tumor necrosis in the recruitment of TANs is not clear. Innate immune cells may differentially react to necrotic cells in terms of chemotaxis e.g. macrophages may show more rapid and sustained attraction toward necrotic cells rather than dendritic cells and neutrophils[49]. Moreover, it is possible to observe large areas of tumor necrosis without neutrophil infiltration (**Figure 3**).

4.2 Classification of cell death.

A number of factors such as hypoxia, starvation or acidosis can determine tumor tissue necrosis. However, the classic notions of apoptosis and necrosis, based on morphologic criteria, have recently been modified. The latest recommendations of the Nomenclature Committee on Cell Death suggest two mutually exclusive types of cell death: accidental and regulated cell death [50-51]. Accidental cell death is an uncontrollable, instantaneous, passive type of cell death that occurs after severe tissue damage due to extreme environmental conditions (e.g. high temperature, elevated pressure, trauma). Morphologically, it is characterized by cellular swelling and consequent collapse of the plasma membrane thereby causing spillage of intracellular contents and inflammatory reaction [51]. Other morphologic changes include generalized swelling of cytoplasm and organelles, nuclear membrane dilatation, nuclear chromatin condensation into small and irregular patches [52]. By contrast, regulated cell death is an active program of cell death that can be modulated by pharmacological agents or genetic interventions both in physiological and pathological conditions. It occurs during chronic or mild exogenous perturbations of cell microenvironment following failure of compensative mechanisms (e.g. autophagy) [50-51]. The term programmed cell death refers to regulated cell death occurring in physiological conditions (e.g. embryonic development, adult tissue homeostasis). A classic example of programmed cell death is apoptosis, which affects single cells or small clusters of cells [51]. Morphologic characteristics of apoptosis include reduction of cell volume (pyknosis), chromatin condensation, nuclear fragmentation (karyorrhexis), plasma membrane integrity until final steps of the process, formation of apoptotic bodies, phagocytosis of apoptotic bodies by macrophages or by adjacent cells (so-called efferocytosis), with no inflammation in most cases [51].

4.3 Subtypes of regulated cell death

Recent studies have however suggested that regulated cell deaths include several subtypes such as necroptosis, ferroptosis, pyroptosis, parthanatos, and mitochondrial permeability

transition–driven regulated necrosis, but not apoptosis [50]. These types of regulated cell death are not mutually exclusive and are not governed by a single molecular pathway, but are characterized by a complex interplay and cross-talk between them [50]. Moreover, they manifest a partial or total necrotic morphology [51]. To date, necroptosis is the best studied form of regulated cell death and is now recognized as an important drug-sensible contributor to tissue injury in many pathologic conditions including ischemia-reperfusion damage, acute inflammatory reactions, and tumor necrosis [50-53]. It is characterized by cellular swelling, rapid membrane permeabilization and concomitant release of damage-associated molecular patterns (DAMPs) into the extracellular space. According to recent studies, DAMPs determine neutrophil infiltration in the tumor stroma [54]. Moreover, neutrophils stimulated by dying cells exert NO/H_2O_2–based cytotoxicity against residual live cells [50-51]. Ferroptosis is a recently described subtype of regulated cell death due to accumulation of lethal lipid ROS produced through iron-dependent lipid peroxidation [55]. Morphologically, it does not show chromatin condensation, characteristically found in apoptosis, nor loss of plasma membrane integrity, as observed in accidental necrosis [50-51]. Instead, it is characterized by mitochondrial shrinkage and increased mitochondrial membrane density [51,55]. These recent revolutionary modifications in the classification of cell death have disclosed new fields of research. It is not surprising that there are a few updated studies focused on the role of regulated cell death in the recruitment of TANs.

4.4 Other Mechanisms of Neutrophil Recruitment in Tumor Stroma

Several literature data suggest that tumor necrosis is not the sole factor responsible for TANs. Immunohistochemical studies have demonstrated that the type of mucin overexpressed by tumor cells is highly correlated with TANs. For example, TANs are prominent in pancreatic and gastric carcinomas with MUC1 overexpression (**Figure 4**) [56-57] and scarce or absent in mucinous carcinomas that overexpress intestinal mucins MUC2 [58]. These data suggest that tumor histologic type may be correlated with TANs. Accordingly, our previous cancer registry study, undertaken to determine the incidence and clinicopathologic features of neutrophil-rich gastric carcinoma in the Messina province (South Italy), revealed an inverse correlation between TANs and mucinous subtype of gastric cancer, classified according to the WHO classification [57]. Mucinous histologic types are recognized morphologically for the presence of extensive extracellular accumulation of mucins that show a strong MUC2 immunoreactivity [58]. Tumor cells discharge MUC2 into mucin lakes that invade tissues and inhibit the host inflammatory reaction [59]. These data explain the scarce neutrophil infiltration in gastric mucinous carcinomas observed in our study (**Figure 5**). In addition to immunohistochemical studies, biomolecular research disclosed the importance of oncogenic activation in the induction of TANs. CXC chemokines [e.g., interleukin-8 (IL-8)], produced by oncogene mutations in cancer cells, may evoke neutrophil infiltration in tumor stroma [60]. One oncogene that has

been strongly linked to the recruitment of TANs is the Ras oncogene. Ji et al. [60] showed a link between the presence of activated K-ras mutations and macrophage and neutrophil predominant inflammation in both murine and human lung tumors. IL8 has been shown to be a transcriptional target for Ras signaling and expression is required for tumor-associated inflammation and angiogenesis in a human tumor xenograft model [61].

Other experimental studies showed that engineered tumors to release interleukins or chemokines in their microenvironment evoke a massive neutrophil infiltration that, often in collaboration with CD8+ T lymphocytes, leads to the rejection of engineered tumor cells and the establishment of significant immunity against wild-type parental tumors [62]. Taken together, literature data suggest that TANs have manifold recruitment causes including tumor necrosis, MUC1 overexpression, and oncogene activation leading to direct cytokine production by tumor cells.

5. Ultrastructural Studies of TANs in Gastric Carcinomas

Our ultrastructural investigations, performed in gastric carcinomas, reiterated the dual face of TANs. At light microscopy, well differentiated gastric adenocarcinomas show intraglandular migration of neutrophils associated to necrotic phenomena of variable extent ranging from single adenocarcinoma cell death to segmental disruption of the epithelial layer of a gland (**Figures 6a, 6b**) up to glandular and stromal necrosis [63-65]. At electron microscopy, we see a spatial relationship between neutrophil intraglandular migration and regulated adenocarcinoma cell death. In Figure 7, one neutrophil is seen in intimate contact with one or a few severely injured adenocarcinoma cells showing increased electron density, loss of microvilli, marked dilatation of nuclear envelope, small condensed chromatin particles, and progressive mitochondrial and endoplasmic reticulum swelling. These ultrastructural changes are different from those described in apoptosis where there is characteristic chromatin condensation and separation of euchromatin and heterochromatin and formation of apoptotic bodies. They are also different from that described in accidental cell death where there is plasma membrane disruption and cytoplasmic organelle swelling. They manifest partial necrotic ultrastructural features, and therefore are compatible with regulated cell death (**Figure 8**). These ultrastructural observations *in vivo* are similar to that reported in *in vitro* studies where neutrophil cytotoxicity requires physical contact between neutrophils and tumor cells [66]. It remains to be investigated whether regulated cell death is triggered by infiltrating neutrophils or alternatively may be responsible for neutrophil infiltration. This question could be resolved through experimental studies of developing disruptions, as opposed to morphologic static observations of disruptions described above.

6. Emperipolesis and Efferocytosis

Humble, in the 1950s [67], coined the term emperipolesis to describe penetration of lymphocytes in other living cells, both in physiological and pathological settings. During emperipolesis, the migrating cell remains viable and can exit without morphological and physiological abnormalities. Efferocytosis is a term used to describe phagocytosis of apoptotic cells, occurring in embryonic development, organogenesis, tissue repair, atrophy, and inflammation [68-69]. Removal of apoptotic cells is necessary to avoid their disintegration in the tissues via a process known as secondary necrosis which leads to uncontrolled leakage of the dying cells and subsequent chronic inflammatory reaction. Macrophages and dendritic cells are the main cells involved in apoptotic cell removal, including apoptotic neutrophils [68-69]. However, also "neighboring" cells such as epithelial cells, endothelial cells, and fibroblasts, may engulf apoptotic cells [69]. In our previous study, we provided morphologic evidence of apoptotic neutrophil efferocytosis by foveolar epithelial cells in chronic active H. pylori gastritis [70].

7. Entosis and Xeno-Cannibalism

In cytological or histological samples of tumors, pathologists can detect cells with cannibalistic properties. This phenomenon may be suggested by the presence of one or more cytoplasmic vacuoles, possibly containing dying cells, that push the nucleus to the periphery giving it the shape of a crescent moon. Classically, the term cannibalism was used to describe the engulfment of tumor cells by other tumor cells. Recently Overholtzer [71] coined the term entosis to describe a process similar to cannibalism and frequently found in human and experimental tumors, whereby cells become internalized into neighboring cells, forming what are called 'cell-in-cell' structures. In his studies, he demonstrated that internalized cells initially appear healthy and viable [71]. Over a brief period, some internalized cells are able to escape, but most cells die through a form of cell death which is distinct from apoptosis as dying cells are negative for cleaved caspase-3, and do not exhibit condensed or fragmented nuclei. Instead, LAMP1, a lysosomal membrane protein, localizes around dying cells and acidification occurs at the earliest stages of death, suggesting lysosomal involvement [71]. Recent reports have shown tumor cell phagocytosis of normal cells (xeno-cannibalism) such as neutrophils, lymphocytes, and erythrocytes [72-75]. These new observations imply that cannibal tumor cells do not distinguish between normal and sibling neoplastic cells.

In literature, there is some confusion about the terms emperipolesis, entosis, cannibalism and xeno-cannibalism [76-77]. In our opinion, they must be used appropriately remembering the neoplastic or non-neoplastic context in which they occur. The main distinctive characteristics of emperipolesis, efferocytosis, entosis, and xeno-cannibalism are summarized in Tables 1a and 1b. Their light microscopic identification in sections stained with hematoxylin-eosin (H&E) sometimes requires ancillary techniques such as caspase

immunohistochemistry, electron microscopy, and TUNEL assay which is based on enzymatic incorporation of labelled nucleotides at sites where DNA fragmentation has occurred. For example, we recently provided light microscope, immunohistochemical and ultrastructural evidence of neutrophil xeno-cannibalism by tumor cells in high grade gastric carcinomas as well as in micropapillary gastric carcinomas (**Figure 9**) [72,78-79]. At the light microscopic level, intra/interepithelial neutrophils showed apoptotic changes such as pyknotic nuclei and cell shrinkage. TUNEL staining documented apoptotic neutrophils in cytoplasmic vacuoles of tumor cells. Electron microscope, a fundamental tool not only to identify apoptosis, but also to discern inter- or intraepithelial neutrophil localization, confirmed the presence of large heterophagosomal vacuoles containing apoptotic neutrophils. Various phases of apoptotic changes were documented in these neutrophils. Ultrastructural signs of early apoptosis included nuclear chromatin separation into dense and electron lucent areas, rounded nuclear profiles, preservation of cytoplasmic granules, and maintenance of cell membrane integrity. Late apoptotic morphology was characterized by cell shrinkage, tightly packed cytoplasmic granules, and uniform collapsed nucleus (**Figure 10**). Secondary degeneration of apoptotic neutrophils in the phagocytic vacuoles of tumor cells included cellular swelling, electron-lucent cytoplasm, vacuolization and indiscernible cell membrane.

The phenomenon of neutrophil xeno-cannibalism by tumor cells may have a series of pathobiological consequences. It has been suggested that the presence of cannibalized cells may interfere with cell mitosis, leading to non-genetic polyploidy [80]. Phagocytosis of neutrophils by tumor cells may constitute a sort of “feeding” activity. Tumor stroma contains malformed microvasculature that contributes to tumor hypoxia, acidosis, and increased interstitial fluid pressures [81]. Thus, independently of microvasculature, tumor cells cannibalizing neutrophils find nutrients useful for their survival. The phenomenon of neutrophil xeno-cannibalism by tumor cells represents an example of protumor activity of TANs, particularly frequent in high grade gastric carcinomas including micropapillary carcinomas.

8. Prognostic Impact of TANs

The prognostic significance of TANs remains controversial. In our previous study on gastric carcinomas, TANs were morphologically identified by H &E stain and manually counted [82]. The multivariable analysis of possible interaction effects of the clinicopathological factors with TANs revealed that female patients with a moderate or extensive amount of TANs had about a 39% reduction in their risk of mortality, whereas no correlation with outcome of male patients was found [82]. A possible explanation for the interaction between TANs and female patients is that sexual dimorphism exists in the immune response [83]. Both humoral and cell-mediated immunity are more active in females than in males, and steroid gonadal hormones may play an important role in regulating this response [84]. These observations suggest the possibility of an inflammatory (neutrophil) and gender-dependent host natural

cytoxicity in the microenvironment of gastric carcinomas. Subsequently, other studies using immunohistochemical stainings (CD66b, myeloperoxidase and CD15) to identify TANs showed discrepant results. Negative (renal [85], hepatic [45,86], colorectal [87], and gastric carcinomas [88-89]), and positive (colorectal carcinomas [47, 90-94]) correlation with patient prognosis have been described in recent publications. These conflicting results may be due to different methods used in quantifying TANs. In several reviews, shift from morphological to immunohistochemical markers was suggested, including CD15, myeloperoxidase and CD66b [95-96]. Nevertheless, both morphological and immunohistochemical methods have their advantages and disadvantages. Galdiero et al. [93] showed that antibodies against myeloperoxidase were not specific for neutrophils, as also monocytes and immature macrophages stained. CD66b is expressed both on human neutrophils and eosinophils and is recognized as a granulocyte "activation marker" [97]. CD15 is expressed on the surface of leukocytes, mainly in neutrophils, eosinophils, and part of monocytes, and do not reflect the activation status of neutrophils [98]. In addition, CD15 has been demonstrated to be expressed occasionally on tumor cells [93].Therefore, CD15 and CD66b are not specific markers for neutrophils, and light microscope analysis of H&E stained sections remains fundamental to distinguish neutrophils from other inflammatory cells. Given that the different markers used to identify TANs (CD66b, CD15 and cell morphology by H&E stain) may explain contradictory results in prognostic studies of TANs, it is desirable that an optimal combination of markers (i.e. morphology with immunohistochemistry for CD66b) be used in future studies.

Recent studies concerning the role of TANs in human colorectal carcinomas merit further discussion. Berry et al. [91] using morphology and manual counting of TANs in colorectal carcinomas, obtained similar results to ours performed on gastric carcinomas. In particular, they show that in women there was a trend towards better overall survival in all patients with high TAN counts suggesting a potential for different roles for TANs in men and women with colorectal carcinoma [91]. Moreover, higher TAN counts in Stage II patients are associated with a nearly 3-fold increase in overall survival compared to patients with low TAN [91]. The favorable prognostic significance of TANs in colorectal carcinomas is confirmed in two recent studies using CD66b immunohistochemistry as a neutrophil marker. Wikberg et al. [47] have studied the prognostic role of infiltrating neutrophils at different intratumoral subsites including the invasive front, the center of the tumor, and in the tumor epithelium of colorectal carcinomas. Expression of the neutrophil marker CD66b was assessed by immunohistochemistry in 448 archival human tumor tissue samples from patients surgically resected for colorectal carcinomas. They found that high infiltration of CD66b-positive cells in the tumor front is a favorable prognostic factor in stages I-II colon cancers [47]. Galdiero et al [93] used disease-specific and disease-free survival as their endpoints and found that the positive prognostic effect for high TAN counts extended to patients with all stages of disease. TAN density dramatically decreases in Stage IV patients as compared to Stage I-III. They

showed that prognostic significance of TANs can be influenced not only by clinical stage but also 5-fluorouracil (5-FU)-based chemotherapy. In particular, higher TAN density was associated with better response to 5-FU-based chemotherapy [93]. Thus, assessment of TAN infiltration may not only be useful for prognostic informations, but may also have important therapeutic implications, in particular for identifying patients likely to benefit from 5-FU-based chemotherapy. I would like to take the opportunity to stress the *favorable prognostic significance of TANs in gastrointestinal cancer* [82,91-94,100] and its evaluation using rigorous quantitative methodology.

9. Conclusions

Understanding the role of TANs in gastric carcinomas remains incomplete, but studies continue to accumulate. What is certain is that neutrophils are not accidentally present in the tumor stroma, rather they play an active role in tumor growth. Previous studies have suggested positive or negative correlation with patient prognosis. In part, these conflicting results may be due to different methods (morphology vs immunohistochemistry) in quantifying TANs. At the same time, experimental studies reveal antitumoral (N1 phenotype) and protumoral (N2 phenotype) functions of TANs. These data should not necessarily be interpreted as demonstration of two distinct subpopulations of TANs. It is also possible that protumoral and antitumoral neutrophils are two extremes of a spectrum of a sole functional state. Based on recent literature and our own data, this neutrophil functional plasticity correlates strictly with clinicopathological parameters such as gender, tumor stage, intra/peritumoral localization of TANs, and response to chemotherapy. In Table 2, we summarize studies concerning the role of TANs in correlation with clinicopathological parameters. These data suggest that, in particular conditions,TANs represent an antitumoral mechanism that should to be documented in routine pathology and promoted therapeutically. It would also be desirable for pathologists to be involved more and more in determining the type of TAN infiltrate, thereby providing diagnostic and prognostic information as well as suggesting appropriate immune-chemotherapies for each patient.

10. Tables

Table 1a: Cell-in-cell structure in both physiological and pathological (non-neoplastic) conditions

EMPERIPOLESIS	EFFEROCYTOSIS
Migration of a cell in the cytoplasm of another	Engulfment of apoptotic cells by macrophages, dendritic cells or adjacent epithelial/mesenchymal cells
During emperipolesis migrating and host cell remain viable	Removal of apoptotic cell commonly occurs in non-neoplastic tissue

Table 1b: Cell-in-cell structure in tumors.

ENTOSIS	XENO-CANNIBALISM
Engulfment of a tumor cell in the cytoplasm of another tumor cell	Phagocytosis of an inflammatory cell by a tumor cell
During entosis engulfed cell is degraded by lysosomal enzymes	During cannibalism engulfed inflammatory cell shows apoptosis

Table 2: Relationship between clinicopathological factors and bipolar prognostic role of TAN.

CLINICOPATHOLOGICAL CONDITIONS	PROGNOSTIC CORRELATION OF TAN	PROGNOSTIC CORRELATION OF TAN
GENDER	FAVORABLE PROGNOSIS IN FEMALES WITH GASTRIC OR COLORECTAL CARCINOMAS WITH HIGH TAN	NO CORRELATION WITH PROGNOSIS IN MALE OPERATED FOR GASTRIC OR COLORECTAL CARCINOMAS
STAGE OF TUMOR	IN STAGE II COLORECTAL CARCINOMAS HIGH TAN IS RELATED TO BETTER PROGNOSIS	LOW TAN IS FOUND IN STAGE IV COLORECTAL CARCINOMAS
INTRA-PERITUMORAL TAN	HIGH PERITUMORAL TAN SHOWS FAVORABLE PROGNOSIS IN STAGES I-II COLORECTAL CANCERS	INTRATUMORAL TAN IS NOT IN RELATION WITH PROGNOSIS IN COLORECTAL CANCER
5-FLUOROURACIL-BASED CHEMOTHERAPY	HIGH TAN ASSOCIATED WITH BETTER RESPONSE TO CHEMOTHERAPY	LOW TAN ASSOCIATED WITH POOR RESPONSE TO CHEMOTHERAPY

11. Figures

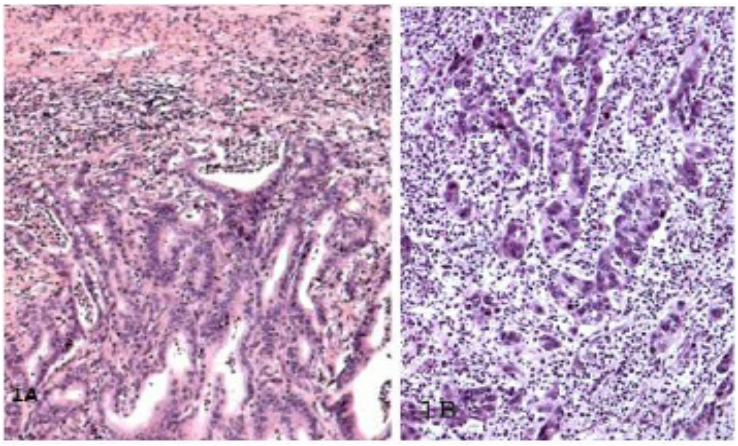

Figure 1
A: TANs are mainly seen at the front of neoplastic tissue. H&E X 100
B: Numerous TANs in the center of tumor. H&E X 100

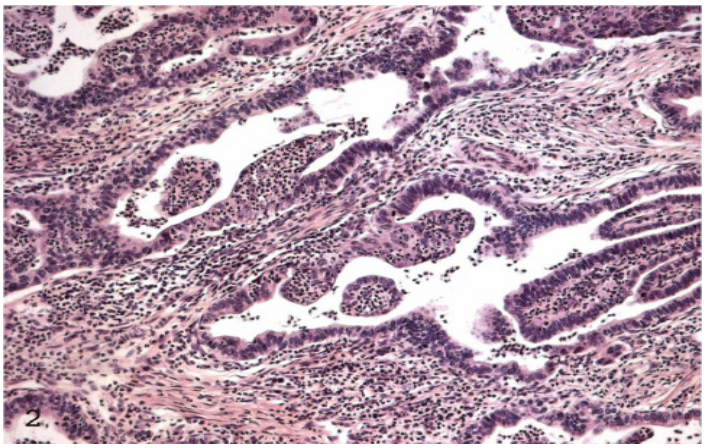

Figure 2: Gastric adenocarcinoma with numerous intraepithelial neutrophils. H&E X 100

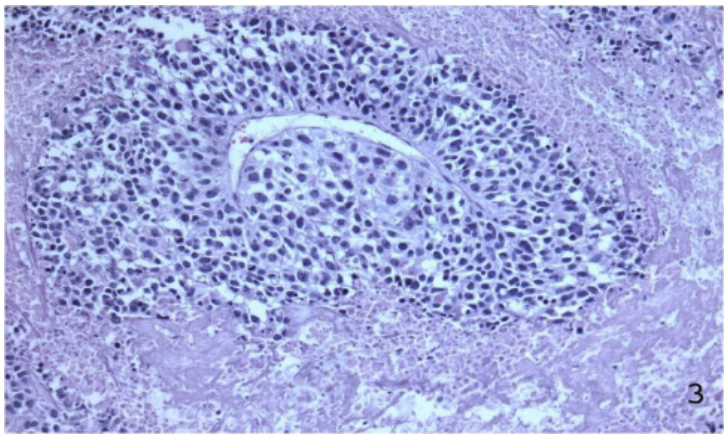

Figure 3: Large areas of tumor necrosis without neutrophil infiltration. H &E x 100

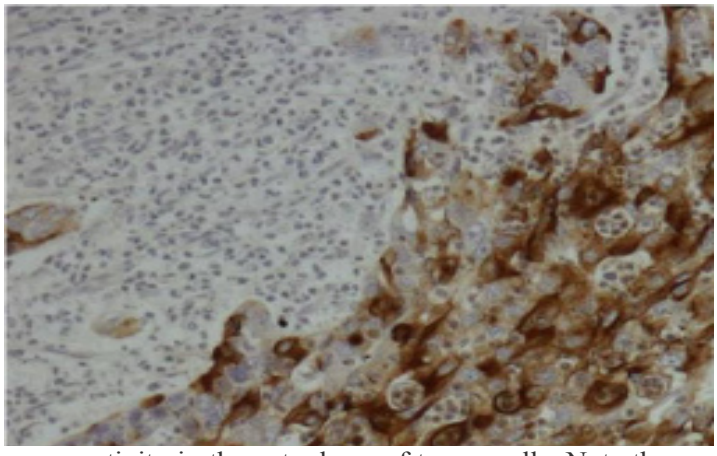

Figure 4: Strong MUC1 immunoreactivity in the cytoplasm of tumor cells. Note the presence of numerous TANs. X 200

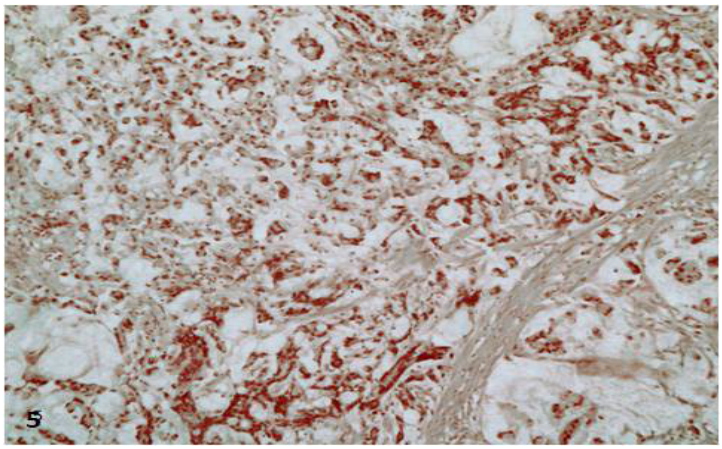

Figure 5: Mucinous adenocarcinoma of the stomach. Note the absence of neutrophils. H&E X100

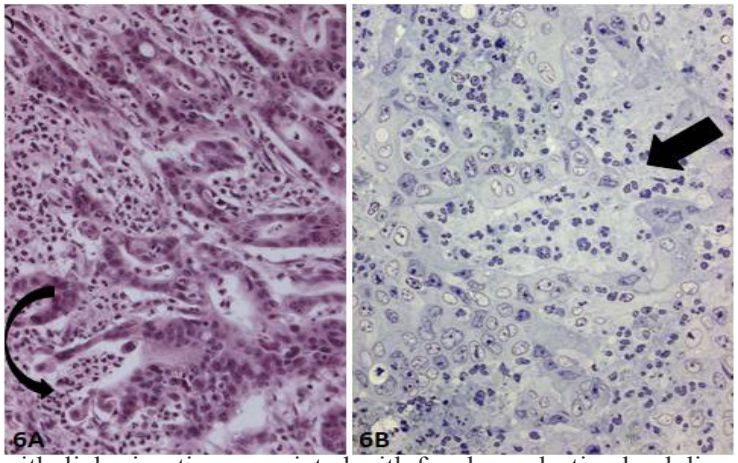

Figure 6A: Neutrophil transepithelial migration associated with focal neoplastic gland disruption (curved arrow). H&E X 10 B: Semi-thin section showing numerous TANs and break in continuity of adenocarcinoma gland (arrow). Giemsa X 200

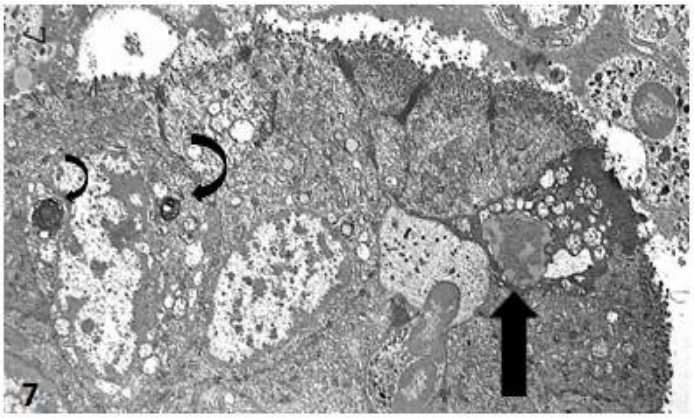

Figure 7: Neutrophil in contact with an adenocarcinoma cell showing chromatin condensation, loss of microvilli, enlarged mitochondria, and dilatation of nuclear envelope (arrow). Note some adjacent tumor cells containing autophagic vacuoles in their cytoplasm (curved arrows). X 8000

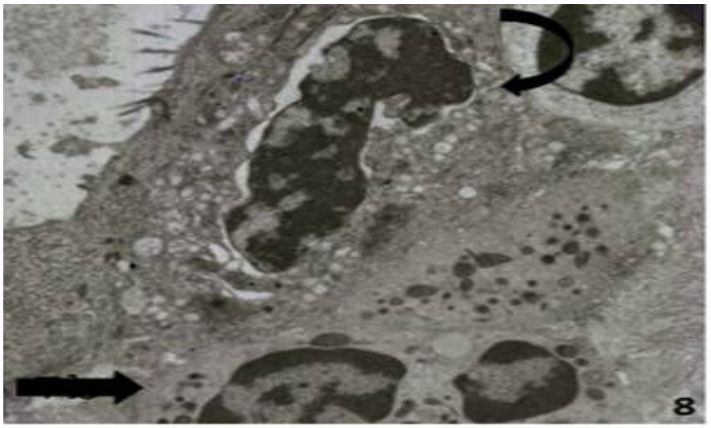

Figure 8: Neutrophils are near adenocarcinoma cell showing convoluted nucleus, marked chromatin condensation, dilatation of nuclear envelope. X 8 000

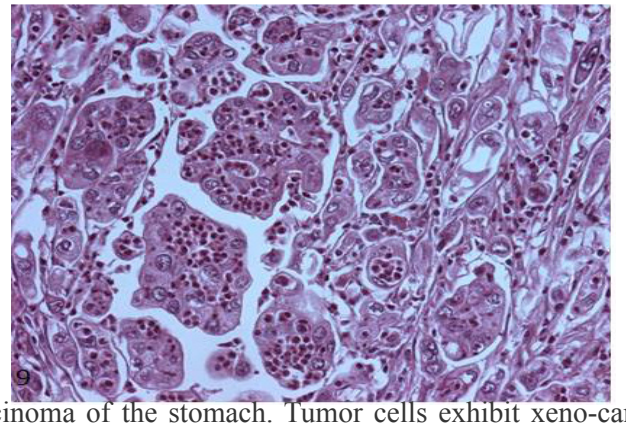

Figure 9: Micropapillary carcinoma of the stomach. Tumor cells exhibit xeno-cannibalism of neutrophils. H&E X 100

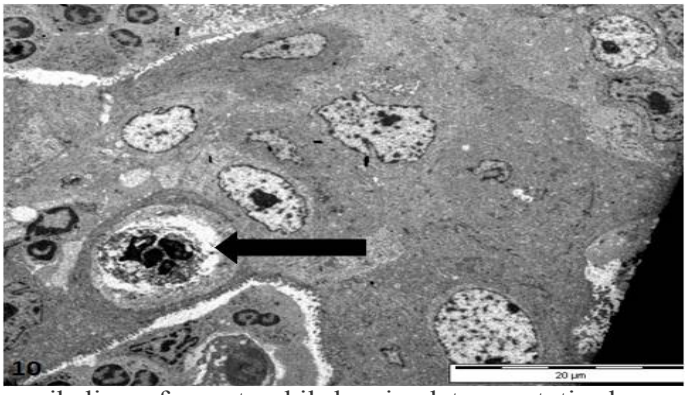

Figure 10: Tumor cell xeno-cannibalism of a neutrophil showing late apoptotic changes. X 4 000

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