14

Gastric Carcinoma Neoadjuvant and Adjuvant Therapy

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1. Introduction

1.1 Epidemiology

In the last 80 years, the incidence of gastric cancer and gastric cancer-related mortality has decreased significantly. However, gastric cancer is the 4th most common cancer and the 2nd common cause of cancer associated mortality in the world (Crew, K.D. Neugut, A.I., 2006, Ferlay, J., et al., 2010, Ferlay, J., et al., 2010, Jemal, A., et al., 2010, Krejs, G.J., 2010, Malvezzi, M., et al., 2010, Sasako, M., et al., 2010, Shin, H.R., et al., 2010). Gastric cancer according to anatomic location in the stomach, proximal (cardia) and distal (noncardia) is divided into 2 groups. Although decreasing, distal located tumors are still the most common type in developing countries. While there is an increase in proximal located tumors, the distal located gastric cancers have been decreasing in western societies (Ferlay, J., et al., 2010, Krejs, G.J., 2010, Malvezzi, M., et al., 2010). More than 90% of gastric cancers are adenocarcinomas and can be either intestinal, or diffuse type (Crew, K.D. Neugut, A.I., 2006, Krejs, G.J., 2010).

The incidence vary significantly throughout the world. More than half of all gastric cancers in the world are seen in eastern Asia (Sasako, M., et al., 2010). Korea and Japan had the highest incidence countries. While its incidence is 60/100.000 for men and 25/100.000 for women in Korea and Japan (Long, N., et al., 2010), it is around 5/100.000 for Australia and New Zealand (Crew, K.D. Neugut, A.I., 2006, Ferlay, J., et al., 2010, Krejs, G.J., 2010, Malvezzi, M., et al., 2010, Sasako, M., et al., 2010, Shin, H.R., et al., 2010). Often seen in whites aged 60-80, the male to female ratio is 2:1, which rises up to 5:1 for proximal tumors (Krejs, G.J., 2010). The main risk factors related to the development of gastric cancer are Helicobacter pylori infection, dietary factors, tobacco use and obesity (Crew, K.D. Neugut, A.I., 2006, Krejs, G.J., 2010, Sasako, M., et al., 2010). Having been the most important cancer-related mortality in the United States in the 1930s for both sexes, its incidence and mortality rates have dramatically decreased over the years. For the year 2010, 21.000 new cases and 11.000 deaths from stomach cancer are estimated in the United States (Jemal, A., et al., 2010). As the 4th most common cause of cancer-related deaths, gastric cancer incidence and mortality rates among the European countries also show significant variations (Ferlay, J., et al., 2010, Krejs, G.J., 2010, Malvezzi, M., et al., 2010). The incidence of stomach cancer in men

is 8/100.000 and in women 3-4/100.000 in European Union (EU) countries. For Russia, these rates are 25 and 10 and for United Kingdom (UK) 5-6, and 2-3, respectively. Although decreased in major European countries, mortality rates still high in eastern and southern Europe with an estimated new cases of 150.000 and gastric cancer-related mortality 116.000 for the year 2008 (Ferlay, J., et al., 2010).

1.2 Surgical therapy

There is no doubt that the only curative treatment option for gastric cancer is gastrectomy and regional lymph node dissection (Swan, R. Miner, T.J., 2006, Tanizawa, Y. Terashima, M., 2010), although the most appropriate surgery and lymph node dissection are still controversial. The debate about surgical approach and extent of lymph node dissection continuing. In early gastric cancer, which is confined to the mucosa or submucosa, in Japan and Korea in particular, endoscopic mucosal dissection and endoscopic submucuosal resection is the usual management (Deprez, P.H., et al., 2010, Kim, J.J., et al., 2007).

Although there are some discussions, subtotal gastrectomy and total gastrectomy is considered to be similar in terms of survival. The complex lymph nodes of stomach are classified by Japanese Gastric Cancer Association. According to this classification regional lymph nodes are divided to 3 groups according to the location of the primary tumor and lymph node dissection is separated into the D0, D1, D2 and D3. Perigastric lymph nodes have been recognized as D1 and the ones around the main branches of the celiac axis as D2 (Japanese Gastric Cancer, A., 1998). The extent of lymph node dissection in gastric cancer surgery is one of the most controversial issues. D2 dissection was performed as a standard approach in Japan, Korea, and some Western countries. D1 dissection is done in many western countries. One of the most well-known studies on this subject is the work of Dutch Gastric Cancer Group. In this study comparing D1 and D2 dissections, a 5-year overall survival and risk of relapse were similar, but perioperative mortality and complication rates were statistically significantly higher in D2 arm (Bonenkamp, J.J., et al., 1999). In a meta-analysis, the benefit of the addition of paraaortic lymphadenectomy (PALD) to D2 dissection was discussed and concluded that additional PALD didn't show survival benefit and was evaluated as less secure (Chen, X.Z., et al., 2010).

D2 dissection and D2 with PALD were compared. While surgery related complication rate were similar between D2 and PALD groups, 5-year overall survival rates were 69.2% in D2 arm and 70.3% in PALD arm [HR (hazard ratio) 1.03, CI (confidence interval) 0.77-1.37, p = 0.85] (Sasako, M., et al., 2008).

The 15 year results of Dutch study was recently published. The median follow-up was 15.2 years. D1 arm had higher locoregional relapse rate and higher gastric cancer related death rate (182, 48%) than D2 arm (123, 37%) (p =0.01). However, the overall survival rate of the D1 arm at 15 years (21%, 85 of 380) and D2 arm (29%, 98 of 331) were similar (p = 0.34) (Songun, I., et al., 2010). You can see key elements of related trials in Table 1.

In the meta-analysis of Yang and colleagues, it was shown that splenectomy didn't have benefit and is not recommended as a routine practice (Yang, K., et al., 2009). However, current National Comprehensive Cancer Network (NCCN) guideline recommends D1 (perigastric lymph nodes) and D2 (along in with named vessels of celiac axis) dissection, with a goal of at least 15 lymph nodes removed at moderate to high volume centers (Ajani, J.A., 2011). Although D2 procedure has a higher postoperative mortality and morbidity, it is being applied as a standard approach with confidence at many large centers.

Study	Intervention	Patients (n)	Postoperative Morbidity	Postoperative Mortality	5-Year Survival
Dutch trial (1989-1993)	D1 vs. D2	380/331	25.0%/43.0% (p<0,001)	4.0%/10.0% (p<0,004)	45.0%/47.0%, HR 1.00 (95% CI, 0.82-1.22)
MRC trial (1987-1994)	D1 vs. D2	200/200	28.0%/46.0% (p<0,001)	6.5%/13.0% (p=0,04)	35.0%/33.0%, HR 1.10 (95% CI, 0.87-1.39)
Taiwanese trial	D1 vs. D3	110/111	7.3%/17.1% (p<0,012)	0%/0%	53.6%/59.5%, HR 0.49 (95% CI, 0.32-0.77)
IGCSG trial (1999-2002)	D1 vs. D2	76/86	10.5%/16.3% (p<0,29)	0%/1.3% N.S	Under analysis

Table 1. Major randomized controlled trials comparing D1 with D2/D3 (Tanizawa, Y. Terashima, M., 2010)

1.3 Prognostic factors and relapse pattern

Based on 10 year results of the "German Gastric Cancer Study," (Siewert, J.R., et al., 1998) they evaluated prognostic factors and they showed that lymph node ratio (ratio between positive and removed nodes; p<0.0001), residual tumor category (R0, Rl, R2; p <0.0001), pT-category (pTl, pT2, pT3 and pT4; p<0.0001, postoperative complications (p<0.0001), distant metastases (MO, Ml; p=0.003) affected prognosis. In a prospective multicenter study; it was shown that nodal status, depth of invasion, limited or extended lymphadenectomy (D1 vs. D2-D3), tumor location (lower vs. upper) and age were independent predictors of recurrence (Marrelli, D., et al., 2005). It was also shown that T (T2 vs. T3, risk ratio 3.55, 95% CI 1.98-6.44 and p: 0.001) and histological type (intestinal vs. diffuse/mixed, risk ratio 2.11, 95% CI 1.25-2.95 and p: 0.021) were independent prognostics indicator in node negative gastric cancer patients (Baiocchi, G.L., et al., 2010). Depth of tumor invasion and nodal involvement are considered the most important prognostic factors (Marrelli, D., et al., 2005).
Although in many cases surgical treatment is the primary treatment, usually locoregional, hematogenous, and peritoneal recurrences are seen and in patients with developing relapse an effective treatment option isn't available (Marrelli, D., et al., 2005). Studies have demonstrated that at least half of all patients who undergo curative resection will have locoregional, peritoneal or distant recurrence (Table 2) (Baiocchi, G.L., et al., 2010, Bonenkamp, J.J., et al., 1999, Buzzoni, R., et al., 2006, D'Angelica, M., et al., 2004, de Manzoni, G., et al., 2003, Kattan, M.W., et al., 2003, Marrelli, D., et al., 2005, Otsuji, E., et al., 2004, Wang, S.Y., et al., 2009), meaning that surgery alone was unable to eradicate all locoregional disease in the majority of patients.
Therefore in addition to surgical resection, the need for systemic and local therapies are apparent. Various preoperative, perioperative and postoperative regimens, chemotherapy (CT), radiotherapy (RT) or combining therapy, have been designed to eradicate microscopic disease.

Reference	Types of relapse (%)			
	Locoregional	Peritoneal	Distant	Multiple-sites
(Marrelli, D., et al., 2005)	23.7	16.2	17.2	7.8
(Buzzoni, R., et al., 2006)	15.8	N.S	34.5	N.S
(Otsuji, E., et al., 2004)	16.0	54.0	31.0	N.S
(Wang, S.Y., et al., 2009)	9.5	23.3	20.6	46.6
(de Manzoni, G., et al., 2003)	32.7	18.1	40	9
(D'Angelica, M., et al., 2004)	25.9	13.6	28.1	32.5
(Sakuramoto, S., et al., 2007)*	11.5	15.8	11.3	N.S.
(Macdonald, J.S., et al., 2001)*	29.0	72.0	18.0	N.S.

N.S.: not specified *Site of first relapse,

Table 2. Type of relapse after curative resection

The majority of patients with gastric cancer are diagnosed at advanced stages. Even in patients are diagnosed at an early stage, 5-year survival rate of patients undergoing surgery alone is low. While the 5 year survival rates are about 70.0% in patients with stage IA, it is 20.0% in patients with stage III (Edge, S. Byrd, D., 2010). Therefore, it is clear that treatments in addition to surgery for gastric cancer are needed. For this reason, a lot of studies in terms of neoadjuvant, perioperative, or adjuvant RT, CT or combined approaches have been tried.

1.4 Possible therapeutic strategies to improve outcome of surgical therapy

CT, RT or combinations of the 2 can therotically be applied before (neoadjuvant) or after (adjuvant) the curative surgery. Being applied earlier in time, neoadjuvant therapy is expected to down stage the disease and increase the rate of curative resection and eradicate possible micrometastases, which are undetectable at the beginning of the treatment. In addition, pre-surgical patients usually have better performance status and can be expected to tolerate treatments better. However on the other hand, patients with initially resectable disease could loose their chance of curative surgery and postsurgical mortality may be increased. One other pitfall of neoadjuvant therapy is imperfectness of clinical staging. There is a possibility to give unnecessay oncological treatments to patients with very early stages of cancer who would not have otherwise receive based on pathological staging . Prior to surgery, yet the normal anatomy and blood flow, target volumes of RT could be more easily detected. However, more patients have metastatic disease at surgery than patients undergoing preoperative reviews. Two randomized important studies on this subject were the Magic and Holland trials (Cunningham, D., et al., 2006, Hartgrink, H.H., et al., 2004).

In the adjuvant setting, pathological staging is known. There is no danger of giving unnecessary treatment. However, patients can tolerate adjuvant therapies less and CT or RT could not be applied at effective doses. In addition, blood flow to the gastric bed may be decreased after surgery which leads to tissue hypoxia. Hypoxic tumor cells do not proliferate to the extend at which non-hypoxic tumors do. Since many chemotherapeutics and RT are more effective on hypoxic cells, adjuvant therapeutic strategies may be less effective than expected.

2. Neoadjuvant trials

2.1 Neoadjuvant radiotherapy

Neoadjuvant randomized clinical trial evaluating the efficacy of RT alone is limited. Zhang et al. randomized 370 patients with *gastric adenocarcinoma of cardia* to surgery alone or RT and surgery group. In the RT arm patients, underwent surgery 2-4 weeks after 40 Gy. The rate of tumor resectability and ratio of T2 tumor were more in RT arm with 11.0% decrease of T4 tumors. Five- and 10-year survival rates for RT plus surgery and surgery alone groups were 30.1%, 19.7% and 20.2%, 13.3%; respectively and these differences were statistically significant. No significant difference was observed between 2 group in term of surgical complication rates (Zhang, Z.X., et al., 1998).

In another study preoperative RT in resectable gastric cancer, there were 51 patients in both RT plus surgery and surgery alone arms and the total doses of RT was 20 Gy and was given in 5 fractions. Although, statistically insignificant, 5- and 10-year survival rates were 39.0%, 32.0% and 30.0%, 18.0% for the preoperative RT and surgery alone groups, respectively. Although concentrated preoperative RT was safe, wasn't enough to provide survival advantage (Skoropad, V., et al., 2002).

Fiorica et al. were evaluated 9 randomized trials (with these two above study, 4 neoadjuvant and 5 adjuvant trials). In this meta-analysis; 3-year (HR 0.57, CI 95% 0.43 – 0.76; p= 0.0001) and 5-year (HR 0.62 CI 95% 0.46 – 0.84; p= 0.002) survival advantage were observed with preoperative RT. Although there was increasing trend in postoperative mortality for preoperative RT group, these difference wasn't statistically significant (HR 0.61 CI 95% 0.24 – 1.57; p= 0.31) (Fiorica, F., et al., 2007).

2.2 Neoadjuvant chemo(-radio)therapy

The CT regimens have been used in patients with metastatic disease has led the way for regimens which could be used as neoadjuvant CT. The first randomized controlled neoadjuvant CT trial was Dutch randomized FAMTX (5-Fluorouracil, doxorubicin and Methotrexate) trial. There were 56 patients and FAMTX regimen was used. The ratio of resectability was similar and at median follow-up of 83 months the median survival is 18 months for FAMTX group vs. 30 months in surgery alone group (p=0.17). This trial could not show a beneficial effect of pre-operative FAMTX, even preoperative CT tends to have negative effect (Hartgrink, H.H., et al., 2004). However, it is clear that FAMTX regimen isn't an effective treatment option for today. In addition, fewer patients have been taken than planned in this study, 25.0% of patients did not receive the planned treatment because of toxicity associated with CT.

The MAGIC trial is one of the most important neoadjuvant CT studies. In this study ECF (epirubicin, cisplatin, and infusional 5-fluorouracil) regimen, which is more effective than FAMTX regimen in patients with metastatic disease, was used. ECF CT regimen was compared surgery alone. Patients with resectable adenocarcinoma of the stomach, esophagogastric junction, or lower esophagus were ranomized to either perioperative CT and surgery (250 patients) or surgery alone (253 patients). CT consisted of 3 preoperative and 3 postoperative cycles of intravenous epirubicin (50 mg per square meter of body-surface area) and cisplatin (60 mg per square meter) on day 1, and a continuous intravenous infusion of fluorouracil (200 mg per square meter per day) for 21 days (Cunningham, D., et al., 2006). Of patients, 90.7% completed preoperative CT, but only 103 of 208 (49.5%) who completed preoperative CT and surgery also completed postoperative treatment. The curative resection rates were similar; 69.3% in the perioperative CT group and 66.4% in the surgery group. There was a greater proportion of stage T1 and T2 tumors and less advanced

nodal disease in the perioperative-CT group. The perioperative-CT group had a higher likelihood of overall survival (hazard ratio for death, 0.75; 95% CI, 0.60 to 0.93; p= 0.009; 5-year survival rate, 36% vs. 23%) and of progression-free survival (hazard ratio for progression, 0.66; 95% CI, 0.53 to 0.81; p<0.001).

3.1 Adjuvant chemotherapy

Numerous clinical trials concerning adjuvant CT for gastric cancer have been conducted with different CT regimens. The results of adjuvant CT trials are conflicting as well, majority being negative with disparities between asian and western ones. Geographic

Author	Patient (n)	Neoadjuvant approach	PR %	pCR %	R0 resection %	OS (months)	OS for R0 resection patients (months)
(Menges, M., et al., 2003)	25	3 or 4 cycles of C, 5-FU, FA	73.0	0	65.0	15.5	23.0
(Schuhmacher, C.P., et al., 2001)	42	3 or 4 cycles of Et-D-C	N.S.	0	73.8	19.1	28.4*
(Ajani, J.A., et al., 2006)	43	2 cycles of induction C, 5-FU, FA followed concurrent RT and weekly infusional 5-FU	N.S.	26.0	77.0	23.2	N.R.
(Hartgrink, H.H., et al., 2004)	59 (29 vs.30)	4 cycles of *FAMTX* vs. surgery alone	32.0#		62.0 vs. 63.0	18.2 vs.30.3	30.0 vs. 66.0
(Biffi, R., et al., 2010)	69 (34 vs. 35)	4 cycles of T-C-5FU Arm A (preoperative) Arm B (postoperative)	55.0	11.7	85.0 vs. 91.0	N.S.	N.S.
(Schuhmacher, C., et al., 2010)	144 (72 vs.72)	2 cycles of C, 5-FU, FA vs. surgery alone	5.8	30.4	81.9* vs.66.7	64.6 vs. 52.5	N.S.
(Cunningham, D., et al., 2006)	503 (250 vs. 253)	3 preoperative and 3 postoperative cycles of E, C, 5-FU vs. surgery alone	N.S.	N.S.	69.3 vs. 66.4	36.0 vs. 23.0* (5 year survival rate)	N.S.

*Statistically significant, C:cisplatin, FU:fluorouracil, FA: folinic asid, RT: radiotherapy, D: doxorubicin, Et:etoposide, N.S.: not specified, N.R.:not reached, MTX: methoterxate, #PR or pCR, PR: partial response, pCR: pathologic complete response, E:epirubicin, T:docetaxel, *FAMTX:* fluorouracil, doxorubicin, methoterxate

Table 3. Major randomized controlled Neoadjuvant trials

variation, small sample sized studies, differences in the surgical techniques account for these conflicting results. However, this does not mean that adjuvant chemotherapies are useless. Compared to current counterparts, CT regimens used in those old studies are relatively-weaker regimes. Many studies are undepowered. Many meta-analyses investigating the role of adjuvant CT for gastric cancer have been performed to overcome such inconsistencies.

Author	Year	No. of studies	Patients	OR/HR (95%CI)
(Hermans, J., et al., 1993)	1993	11	2096	0.88 (0.78-1.08)
(Earle, C.C. Maroun, J.A., 1999)	1999	13	1990	0.80 (0,66-0,97)*
(Mari, E., et al., 2000)	2000	21	3658	0,82 (0,75-0,89)*
(Liu, T.S., et al., 2008)	2008	23	4919	0,85 (0,80-0,90)*
(Paoletti, X., et al., 2010)	2010	17	3838	0,82 (0,76-0,90)*

OR: Odds ratio, * statistically significant values for survival

Table 4. Meta-analyses of adjuvant chemotherapy in gastric cancer

A meta-analysis was conducted on 13 randomized trials of adjuvant CT in gastric cancer concluded that adjuvant CT might produce a small survival benefit with a borderline statistical significance (Earle, C.C. Maroun, J.A., 1999). The trials in this meta-analysis were all performed in Western countries. Marie et al reviewed 20 clinical trials of adjuvant CT compared with surgery alone published between 1983 and 1999. Reviewers suggested that CT reduced the risk of death by 18% (HR 0.82, 95% CI: 0.75-0.89) and addition of anthracyclines to 5-FU did not show a statistically significant improvement when compared with other regimens (Mari, E., et al., 2000). The meta-analysis published in 2008 by Liu et al. based on 23 randomized clinical trial included 4919 patients (2441 in the adjuvant CT arm, 2478 in the observation arm). The study showed relative risk on death of 0.85 (95%CI: 0.80-0.90) which favored the survival role of adjuvant CT. The authors of this meta-analysis concluded that NNT (number needed to treat) was 14, indicating that 14 patients would need to receive adjuvant therapy to prevent one death (Liu, T.S., et al., 2008). However, meta-analyses mentioned above were restricted since they were based on the review of the literature rather than original individual patient data. Recently, an individual patient level meta-analysis of randomized control trials was published by GASTRIC (Global Advanced/Adjuvant Stomach Tumor Research International Collaboration) Group. The meta-analysis based on 17 trials (including 3838 patients) comparing adjuvant CT with surgery alone for resectable gastric carcinoma. In the study four groups of CT regimens were defined: 1) monochemotherapy agents 2) fluorouracil, mitomycin C and other therapies without anthracyclines 3) fluorouracil, mitomycin C, and anthracyclines 4) other polychemotherapy regimens. The study revealed statistically significant benefit associated with adjuvant CT both for overall survival (OS) (HR, 0.82; 95% CI, 0.76-0.90) and disease-free survival (DFS) (HR, 0.82; 95% CI, 0.75-0.90, P<.001, for both). There was no significant difference between 4 CT regimens in terms of OS and DFS. The reviewers suggested that, adjuvant fluorouracil –based CT, even as monotherapy, had improved overall survival after

curative resection of gastric cancer (Paoletti, X., et al., 2010). Also in the meta-analyses of Sun et al. the pooled HR for overall survival was 0.78 (95 per cent confidence interval 0.71 to 0.85) in favor of CT (Sun, P., et al., 2009).

S-1 is an orally active combination of tegafur, gimercil and oteracil that has an appropriate bio-availability for using after gastrectomy. The Japanese randomized phase 3 trial assessed the efficacy of S-1 monotherapy as adjuvant CT in resected gastric cancer. In the study conducted by Sakuramoto et al. 1059 patients with stage 2-3 gastric cancer randomized to surgery only or adjuvant therapy with S-1 after extended (D2) gastrectomy. In the interim analysis after median follow-up of 2 years both overall survival and relapse-free survival differed between two groups favoring adjuvant CT arm, so the data and safety monitoring committee recommended early discontinuation of the trial. The study disclosed that the hazard ratio for death in the S1 group, as compared to surgery only group was 0.68 (95% CI, 0.52-0.87, P=0.003) and 3-year overall survival of 80.1% vs. 70.1% respectively. The authors suggested that S-1 was potent adjuvant CT for East Asian patients who underwent D2 dissection for locally advanced gastric cancer (Sakuramoto, S., et al., 2007). After this trial adjuvant CT without radiation therapy has been the standard in Japan.

In conclusion, adjuvant CT may be considered in patients with locally advanced gastric cancer after curative surgery who had not received neoadjuvant treatment and not candidate for chemoradition therapy.

3.2 Adjuvant radiotherapy

One randomized clinical trial evaluated the role of adjuvant RT after curative resection in gastric cancer (without concurrent CT). According to the trial performed by British Stomach Cancer Group 436 patients with resected gastric cancer were stratified to no adjuvant treatment or adjuvant RT or adjuvant CT with adriamycin, 5-FU and mitomycin C. The five year survival rates were as follows: for surgery alone 20%, for surgery plus RT 12.0%, for surgery plus CT 19.0%. No advantage in terms of survival in either adjuvant arm was observed, but RT offered an advantage in reducing local recurrence as compared to surgery only group (local recurrence rates were 27.0% versus 10.0% favoring surgery plus RT (Hallissey, M.T., et al., 1994).

3.3 Adjuvant chemoradiotherapy

Gastric cancer can recur loco-regionally, or systemically. The review from Memorial Sloan-Kettering Cancer (MSKCC) demonstrated patterns of relapse of 1172 patients who underwent potentially curative surgery from July 1985 through June 2000 (D'Angelica, M., et al., 2004). Among 496 patients who had a recurrence, whole data on recurrence was obtained in 367 patients. Loco-regional sites were a component of relapse in 54.0% of patients including the anastomosis, lymph nodes and the gastric bed. Distant sites and peritoneal relapse were documented in 51.0% and 29.0% of patients, respectively. Since adjuvant RT alone did not appear to confer advantage in terms of survival, RT combined with CT was evaluated in randomized clinical trials. The rationale to use CRT in the adjuvant setting in gastric cancer is not only to control loco-regional recurrence but also distant metastases. First, when used concurrently with RT chemotherapeutic agents may act as a radio-sensitizer. Second, CT may improve systemic control by eliminating microscopic distant metastasis. Various mechanisms are responsible for the interaction between CT and RT. Ionizing radiation induces DNA base damage, alkali-labile sites, single-strand breaks, and double strand breaks. Double strand breaks are the most important damage among

them and causes tumor-kill whether remains unrepaired. Chemotherapeutic agents that inhibit DNA repair, including fluorouracil, cisplatin, irinotecan, can improve radiation cytotoxicity synergistically. CT can also act by restraining post-radiation damage repair. The phase of the cell cycle is another determinant of radio-sensitivity. While cells in G2-M phase are most radiosensitive, cells in the S phase of the cell cycle are the most radio-resistant (Terasima, T. Tolmach, L.J., 1961). CT and RT also produce synergistic effect by targeting different phases of the cell cycle when used concurrently. Moreover, drugs such as taxanes has the ability to block the cell cycle at the G2-M phase so that enhances the radiation effect (Tishler, R.B., et al., 1992).

Several randomized trials assessed the effectiveness of chemo-radiation after curative surgery. Dent et al. performed randomized trial including 142 patients with all stages of gastric carcinoma. The patients in Division I (T1-3, N1-2, and M0) were assigned to control and RT plus 5-FU group. Division II (T4, M1) was randomized into three groups; a control group, RT plus 5-FU, thiotepa for six months. After 4.5 year's follow-up the control and treatment groups did not differ with respect to survival rate in neither Division I nor Division II (Dent, D.M., et al., 1979). In the randomized trial conducted by Bleiberg and colleagues, 115 patients who underwent curative and palliative surgery were stratified into four treatment groups. Patients received RT alone or in combination with short-term and/or long term 5-FU infusion. Statistically differences were determined in terms of overall survival but the difference in survival disappeared when comparisons adjusted for prognostic factors (Bleiberg, H., et al., 1989). In the study by Moertel and co-workers 62 patients with resectable but poor prognosis gastric carcinoma were randomized to surgery versus surgery plus adjuvant treatment with 5-FU plus radiation. Although both five-year survival rates and local-regional recurrence favored treatment arm results did not reach statistical significance (Moertel, C.G., et al., 1984).

The largest trial evaluating the use of postoperative chemoradiation was U.S. Intergroup 0116 trial (Macdonald, J.S., et al., 2001). In this study 556 patients with curatively resected gastric or gastroesophageal junction adenocarcinoma (stage Ib through IV M0) were randomized to surgery alone or adjuvant combined chemoradiotherapy (CRT). The adjuvant treatment consisted of one course of 5-FU 425 mg/m2/d and leucovorin 20 mg/m2/d, daily for five days, followed one month later by 45 Gy of radiation during 5 weeks with 5-FU 425 mg/m2/d and leucovorin 20 mg/m2/d on days 1 through 4 and last 3 days of radiation. One month after completion of RT 2 more 5-day cycles of CT (5-FU 425 mg/m2/d plus leucovorin 20 mg/m2/d) were administered. After a median follow-up of 5 years, the median duration of survival was 36 and 27 months in the CRT and surgery-only groups, respectively. The 3-year survival rates were 50% versus 41% favoring adjuvant treatment. The 3-year rates of relapse free survival increased from 31.0% to 48.0% in the CRT group. Improvements both in overall and relapse free survival were statistically significant. Grades 3 and 4 toxic effects (mostly, hematologic and gastrointestinal) occurred in 41.0% and 32.0% of chemo-RT groups, respectively. Three patients (%1) died as a result of toxic effect of the treatment. The extent of the surgical resection was an important issue in the study protocol. Although, D2 dissection was recommended, only 10.0% of patients underwent a D2 dissection, 54.0% of the patients underwent D0 dissection (in which all of the N1 nodes were not resected). When patients relapse patterns were examined, local-regional recurrence was higher in the surgery only group, despite the higher distant metastasis rates detected in the CRT group (statistical assessment of the relapse sites were not included in the study). The study demonstrated that the benefit of CRT in the adjuvant

setting was mainly apparent by reducing loco-regional recurrence. At the end of the study Macdonald et al. suggested that, postoperative CRT should be considered for all patients at high risk for recurrence of adenocarcinoma of the stomach or gastro-esophageal junction who undergone curative resection.

4. Intra-peritoneal chemotherapy

Peritoneal spread of tumor cells is frequently seen in the course of gastric carcinoma. The expected median survival time is approximately 3 to 6 months when peritoneal carcinomatosis and ascites become evident (Sakata, Y., et al., 1998). The rationale to use peritoneal route to prevent and/or treat the peritoneal spread is to deliver higher concentrations of CT within peritoneal cavity without marked systemic toxicity. Several randomized trials assessed the role of intra-peritoneal CT with different aspects regarding the timing of drug administration, the type of chemotherapeutic agents and the impact of hyperthermia. At least two meta-analyses of randomized clinical trials on adjuvant intra-peritoneal CT for curatively resected gastric cancer showed clinical benefit of this treatment. The meta-analysis by Xu and colleagues included eleven trials involving 1161 cases (Xu, D.Z., et al., 2004). All included trials were randomized, controlled trials that compared surgery plus intra-peritoneal CT with or without activated carbon particles with surgery alone. No other adjuvant treatment including oral or parenteral CT, RT or chemo-immunotherapy was used in the adjuvant group. In the study 609 patients were assigned to the treatment group and 552 to the control group. Most of the studies used mitomycin C with or without carbon particles as a chemotherapeutic agent. The pooled odds ratio was 0.51 with a 95% confidence interval (0.40-0.65). Moreover, in the subgroup analysis trials that used intra-peritoneal hyperthermic chemoperfusion or CT with activated carbon particles was more effective than the trials without hyperthermia and carbon particles. The other meta-analysis performed by Yan and coworkers also involved 13 randomized control trials that compared surgery plus intra-peritoneal CT to surgery alone (Yan, T.D., et al., 2007). The trials included patients with locally advanced gastric cancer without distant metastasis. In the study intra-peritoneal chemotherapies grouped in five categories according to the timing of the procedure and whether hyperthermia was used. The 1st group was composed of trials assessing the role of hyperthermic intra-operative intra-peritoneal CT (HIIC). The 2nd group involved trials investigating normothermic intra-operative intra-peritoneal CT (NIIC). The 3rd group was composed of trials exploring the efficiency of early postoperative intra-peritoneal CT (EPIC). The 4th group included combined forms and the 5th group included the trials of delayed postoperative intra-peritoneal CT (DPIC). The study showed significant survival benefit in favor of HIIC (Hamazoe, R., et al., 1994) (HR:0.60; 95% CI;0.43-0.83) and HIIC combined with EPIC (Gao Z, J.Z., Zhou F, 2002, Wei, G., et al., 2005) (HR:0.45;95%CI:0.29-0.68). The improved survival provided by NIIC did not reach statistical significance (Rosen, H.R., et al., 1998, Takahashi, T., et al., 1995, Yonemura, Y., et al., 2001) (HR:0.67;95% CI:044-1.01; p=0.06), no benefit was found either with EPIC (HR:0.64;95% CI:037-1.10) or DPIC (HR:0.89;95% CI:0.51-1.55). The meta-analysis did not show significant difference in perioperative mortality between the 2 arms. The incidence of intra-abdominal abscess was significantly higher among patients in the intra-peritoneal CT arm. Though none of the individual trial showed increased incidence in terms of

neutropenia the meta-analysis found intra-peritoneal chemotherapy associated with increased risk of neutropenia. The authors of the meta-analysis concluded that HIIC with or without EPIC after resection of advanced gastric cancer was associated with improved overall survival at the expense of increased risk of intra-abdominal abscess and neutropenia.

5. Current standard of care in the world

Surgical resection with lymph node dissection is the primary treatment of early gastric cancer. Total gastrectomy is preferred for tumors arising from proximal stomach or tumors infiltrating stomach diffusely. For distal gastric cancers subtotal gastrectomy is procedure of choice due to fewer complications, lower morbidity and similar survival compared with total gastrectomy (Bozzetti, F., et al., 1999). Endoscopic mucosal resection is the standard treatment in Japan for early gastric cancer limited to mucosa without lymph node involvement (Soetikno, R., et al., 2005).

The extent of lymph node dissection still remains to be a matter of debate. Although gastrectomy with D2 lymphadenectomy is the standard treatment in Japan, in Western studies extensive lymphadenectomy have not provided survival benefit when compared with D1 lymph node dissection (Bonenkamp, J.J., et al., 1999). D2 dissection is more and more adopted in western societies.

In United Kingdom and most of the parts of Europe perioperative CT with ECF regimen became the standard of care, based on the results of the MAGIC trial. This approach is also recommended with level 1 evidence in United States (U.S.) for patients with T2 or higher tumors.

The results of INT-0116 trial changed standard of care in United States from observation to chemo-radiation after curative resection of gastric cancer without evidence of metastasis. Patients with T3, T4 or node positive tumors are recommended to be treated with RT (45-50 Gy) concurrent with 5-FU plus 5-FU (with leucovorin) after curative resection in U.S., although this approach has not been accepted in most of Europe and Japan.

In Japanese population adjuvant CT with S-1 was detected to improve survival after gastric resection with D2 lymph-node dissection in stage II-III gastric cancer. Though it seems to be feasible adjuvant treatment option in East Asian patients, there is not enough data to recommend this approach in Western population.

6. Future directions

Despite advances both in adjuvant and metastatic setting, overall survival in gastric cancer remains to be poor. New agents and new schedules which have been proved to be effective are being integrated into trials of neoadjuvant or adjuvant trials. Emerging data from clinical trials evaluating combination chemotherapies and new molecular targeted therapies has shown clinical benefit especially in metastatic disease. The efficacy of these novel therapies should be confirmed in well designed prospective randomized clinical trials.

Newer chemotherapeutic agents, namely taxanes, oral fluoropyrimidines (UFT, S1, capecitabine) and irinotecan have widely searched in advanced stages of gastric cancer. Naturally, it is expected that the most effective and tolerable chemotherapeutic strategies in

the metastatic setting should be evaluated in earlier stages. In the V325 trial by Van Cutsem et al. the combination of docetaxel, cisplatin and 5-FU (DCF), was significantly superior than cisplatin plus 5-FU (CF) in terms of OS, time to tumor progression and response rate (Van Cutsem, E., et al., 2006). In the phase II randomized trial (NEOTAX) DCF combination CT will be evaluated as a neoadjuvant therapy in locally advanced gastric adenocarcinoma (Clinicaltrials.gov number is NCT00343239). The objective of this study is to determine the impact of DCF combination CT on R0 resection rate in gastric cancer. Patient recruitment is over and the first results are expected in January 2012.

In the large CRITICS trial, the question of whether adjuvant CRT with weekly cisplatin and capecitabine after 3 cycles of neoadjuvant ECC (epirubicin, cisplatin and capecitabine) and surgery in comparison with 3 more cycles of the neoadjuvant schedule (clinicaltrials.gov no: NCT00407186). Nearly 800 patients are expected to be recruited and the first results are awaited in 2013.

The rationale to combine targeted therapies with CT is to improve the efficacy with acceptable toxicity. Epidermal growth factor receptor 2 (also known as HER-2) has become important target in gastric cancer. Trastuzumab, a fully humanized monoclonal antibody against HER-2, was recently evaluated in metastatic gastric cancer. In randomized phase 3 ToGA trial patients were randomly assigned to receive trastuzumab plus CT (capecitabine plus cisplatin or fluorouracil plus cisplatin) or CT alone. The study revealed that median overall survival was 13.8 months in those assigned to trastuzumab plus CT as compared with 11.1 months in those received CT alone (HR: 0.74; 95% CI:0.60-0.91; P=0.046). The authors suggested that trastuzumab plus CT substantially improved OS in patients with high expression of HER-2 protein (immunohistochemistry 2+ and FISH + or immunohistochemistry 3+) compared with patients with low expression of HER-2 (immunohistochemistry 0 or 1+ and FISH+). It was also reported that combining trastuzumab with CT did not cause additional toxic effect (Bang, Y.J., et al., 2010). It is currently not known whether the benefit achieved in metastatic gastric cancer will be translated to adjuvant setting. It was also shown that replacing cisplatin with oxaliplatin and fluorouracil with capecitabine is not inferior than the classical ECF (epirubicin, cisplatin, fluorouracil)(Okines, A.F., et al., 2009). A study of capecitabine in combination with trastuzumab and oxaliplatin in patients with resectable gastric cancer, namely TOXAG (Trastuzumab, Oxaliplatin, and Xeloda for Adjuvant Gastric Cancer) was recently designed to evaluate the impact of trastuzumab in adjuvant and adjuvant strategy.

Bevacizumab, recombinant humanized monoclonal antibody that targets vascular endothelial growth factor, was recently studied in combination with irinotecan and cisplatin in patients with metastatic gastric adenocarcinoma in a phase II multicenter study (Shah, M.A., et al., 2006). The study revealed that, time to disease progression improved by 75% in compared to historical controls. Rates of rare but important complications of bevacizumab, namely gastrointestinal perforation and hemorrhage, was also found similar to rates of several recent large advanced phase studies. The authors of this study concluded that bevacizumab could be added to CT safely and was active in the treatment of advanced gastric adenocarcinoma. A randomized phase III trial will assess the safety and efficacy of neoadjuvant and adjuvant CT including epirubicin, cisplatin and capecitabine with or without bevacizumab in patients with untreated resectable gastric or gastroesophageal junction cancer (MAGIC-B Study) (clinicaltrials.gov no: NCT00407186). Planning to have

1100 patients, the results of this study may clarify the role of bevacizumab in adjuvant/neoadjuvant setting.
There are also adjuvant studies exploring the role of S-1, a newer oral fluoropyrimidine analog.

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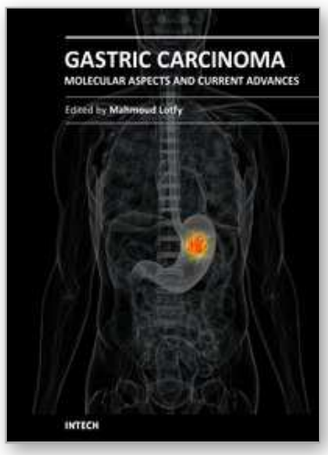

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Gastric cancer is one of the most common tumors worldwide. It has a heterogeneous milieu, where the genetic background, tumor immunology, oxidative stress, and microbial infections are key players in the multiple stages of tumorigenesis. These diverse factors are linked to the prognosis of the gastric cancer and the survival of gastric cancer patients. This book is appropriate for scientists and students in the field of oncology, gastroenterology, molecular biology, immunology, cell biology, biology, biochemistry, and pathology. This authoritative text carefully explains the fundamentals, providing a general overview of the principles followed by more detailed explanations of these recent topics efficiently. The topics presented herein contain the most recent knowledge in gastric cancer concerning the oncogenic signaling, genetic instability, the epigenetic aspect, molecular features and their clinical implications, miRNAs, integrin and E-cadherin, carbohydrate-associated-transferases, free radicals, immune cell responses, mucins, Helicobacter-pylori, neoadjuvant and adjuvant therapy, prophylactic strategy for peritoneal recurrence, and hepatic metastasis.

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