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**302** INVITED

**Optimal treatment for gastric cancer: Tailor made surgery**

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Radical surgical dissection of gastric cancer is the basis of cure in this disease. However, because most patients in the Western world present with advanced stages, surgery alone provides long-term survival in only 20−30% of patients. Western series report locoregional failures in about 60% of patients with positive lymph nodes or involvement of the serosa. This high relapse rate has initiated a whole spectrum of more aggressive treatments which did not result in favorable survival until the introduction of combined chemoradiation in the adjuvant setting.
Prospective randomized trials have investigated the role of more extensive lymph node dissection (D2) in comparison with the standard D1 lymph node dissection in which only the perigastric nodes are removed. In the Dutch Gastric Cancer Group trial, 711 patients treated with curative intent were randomized between D1 and D2 lymph node dissection. After a follow up of 15 years there is now a significant difference in favor of D2 of gastric cancer related mortality. Morbidity (25 vs. 43%;$p < 0.001$) and mortality (4 vs. 10%; $p = 0.004$) however, were significantly higher in the D2 group.
The only study demonstrating an overall survival benefit from extended lymphadenectomy (D3) has been published by Wu et al.
In 2005 the final results of the MAGIC-study on perioperative chemotherapy have been presented. In this large multicentre study patients were randomized between surgery only and 3 cycles preoperative ECF (epirubicin, cisplatin, 5-FU) followed by surgery and another 3 cycles of ECF chemotherapy. This regimen resulted in a 10% higher resectability rate and a significant survival benefit of 13% (23% vs. 36%) at 5 years.
In 2001, with the introduction of postoperative combined chemotherapy, a substantial improvement in survival and locoregional control has been described for the first time. An impressive increase in median overall survival was obtained in the chemoradiotherapy group; 36 months versus 27 months in the surgery only group. More relapse free survival was prolonged from 19 months in the surgery only arm to 30 months in the chemoradiotherapy arm. This postoperative chemoradiotherapy regimen has become standard treatment in the US. Nevertheless this study has been criticized because of suboptimal surgery, concerns about toxicity, an outdated chemotherapy regimen and suboptimal radiotherapy techniques. Indeed, 54% of all patients underwent a D0 lymph node dissection, which in it self could be one factor in undermining survival.
Taken together the abovementioned pivotal MAGIC and SWOG/Intergroup studies, the important question that needs to be answered is whether postoperative chemoradiotherapy improves survival and/or locoregional control in patients receiving neoadjuvant chemotherapy followed by an adequate resection. We therefore conduct a prospective randomized multicenter phase III trial (CRITICS; ChemoRadiotherapy after Induction chemoTherapy In Cancer of the Stomach) addressing this important question. In the adoption of the surgical procedure on the basis of imaging and molecular staging will be discussed.

**303** INVITED

**Perioperative treatment – current standards and next steps**

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Surgery is the main treatment for cancer without distant metastases, however most patients develop recurrences despite R0 resection. Consequently, many attempts have been made to prevent recurrences and improve overall survival. Adjuvant chemotherapy (CT) has not been accepted as standard treatment and is applicable only in 50% of the patients (Braga M. et al Br. J. Surg. 75:477−80 (1988); its benefit is less than 10% increase in overall survival (OS) in the recent and appropriate meta-analyses using, individual data (HR = 0.81; $p < 0.0001$) (Sakamoto J, Paoletti X, GASTRIC. abstract ASCO, JCO 2008 # 4543). The adjuvant chemo-radiotherapy (US standard) is active but has the same drawback as only patients in excellent post-operative nutritional status are able to receive it.
The reasons to develop peri-operative chemotherapy are: low efficacy of adjuvant CT, high percentage of patients unable to receive an adjuvant treatment after gastric surgery, testing CT efficacy before surgery, and possibility of down-staging (Rougier P, et al. Eur J Cancer 1994;30A:1269–75).
Two randomized trials have demonstrated the efficacy of this approach:
– the MAGIC trial has evaluated the impact of the addition of a perioperative chemotherapy (epirubicin, cisplatin and (protracted continuous infusion of 5FU), on the survival of 503 patients with resectable gastro-oesophageal cancer (stomach adenocarcinomas: 74% of patients). It reported an increased overall survival in the group receiving a perioperative chemotherapy with a 5-year survival rate of 36% versus 23% (HR for death, 0.75; $p = 0.009$) and in the progression-free survival (HR for progression or death, 0.66; $p < 0.001$). (Cunningham D, et al. N Engl J Med 2006;355:11−20.)
– The FNLCC-FFCD trial conducted on 224 untreated patients with resectable adenocarcinoma of the lower oesophagus and oesophagogastric junction (74% of cases) or stomach cancer (26% of cases) randomized to receive a preoperative chemotherapy (CS group: 2−3 cycles: 5-fluorouracil over 5 days plus cisplatin 100 mg/m$^2$ on day 1) every 28 days) followed by surgery (n = 113) followed by postoperative chemotherapy in case of efficacy and good tolerance compared to surgery alone (S group; n = 111). The neoadjuvant CT results in a better overall survival (5-year survival rate 38% versus 24%; hazard ratio-HR-for death: 0.69; $p = 0.02$); and of disease-free survival (5-year disease-free survival 34% versus 19%; HR 0.65; $p = 0.003$). In the multivariate analysis of survival, neoadjuvant chemotherapy ($p = 0.01$) and distal site of the stomach cancers ($p < 0.01$) were the only 2 independent prognostic factors. In this trial preoperative chemotherapy significantly improved the curative resection rate (84% *versus* 73%, $p = 0.04$) and its tolerance was acceptable with grade 3/4 toxicity observed in 38% of CS patients (mainly neutropenia) and no increase in postoperative morbidity (Boige V et al; abstract: J Clin Oncol 2007;25:4510; manuscript submitted for publication).

From these two studies we can conclude that for potentially resectable gastro-oesophageal adenocarcinoma, preoperative cisplatin based chemotherapy significantly increased the curative resection rate, disease-free and overall survivals.
The next steps are:
1. to develop better tolerated and more efficient chemotherapy (Cunningham MD, et al. J Clin Oncol 2006;24:LBA4017.) and to test the benefit of adding biologics like antiangiogenic (bevacizumab presently tested in MAGIC2 trial) or tratuzumab in HER2 positive patients.
2. To test the feasibility and efficacy of different combinations of chemo and radiotherapy in preoperative.

**304** INVITED

**Current chemotherapy options for advanced disease**

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Patients with gastric adenocarcinoma present frequently with large, unresectable or metastatic tumours at the time of diagnosis. For these patients, treatment is palliative and, in most cases, options are limited to systemic chemotherapy or supportive care.
Conventional cytotoxic chemotherapy as compared to Best Supportive Care (BSC) can improve the overall survival, quality of life and symptom-free period in carefully selected patients with advanced gastric cancer or gastro-esophageal junction adenocarcinoma. A benefit of a chemotherapy combination has been demonstrated over single-agent regimens in term of overall survival. Many studies evaluate the activity of doublets or triplets. Amongst the agents used in these combination regimens are the fluoropyrimidines (5-FU, capecitabine or S1 in parts of Asia), the platinums (cisplatin or oxaliplatin), the taxanes (docetaxel or paclitaxel), epirubicin and irinotecan. The fluoropyrimidines are often a partner in these combination regimens; it has been shown that 5-FU and capecitabine have a similar activity in advanced gastric cancer. The trials with S1 in Western patients were disappointing. The platinums are also very often used in the combination regimens: several studies have also shown that cisplatin and oxaliplatin have a similar activity. Docetaxel has been studied more extensively than paclitaxel. Adding docetaxel to 5-FU and cisplatin increases the activity (DCF regimen), but also the toxicity. Irinotecan has not been approved for advanced gastric although, it is also active in gastric cancer regimens. Epirubicin is also combined with a fluoropyrimidine and