Today, positive estrogen receptors (ER+) identify women who require endocrine therapy, and HER2/neu positivity those who require trastuzumab and also benefit most from anthracyclines.
Tamoxifen (T) plus ovarian ablation or suppression (OA) or T alone are currently accepted as standard adjuvant endocrine therapies (ET) in young women with ER+ early BC.
The additional benefit of chemotherapy (CT) for premenopausal patients with endocrine-responsive BC who receive combined ET with OA and T (or an aromatase inhibitor) remains an open question.
In the future more sophisticated molecular factors may identify those patients who require ET alone, CT alone, newer biologic therapies, or combinations of these approaches.
CT, ET, and local therapies have the potential to significantly impact both the physiologic health-including future fertility, premature menopause, and bone health-and the psychological health of young women as they face a diagnosis of BC. Better tools and strategies to manage these long-term consequences of the disease and related treatments need to be implemented and monitored and health care professional should systematically address in advance these issues when dealing with young patients.
As many unanswered questions remain, it is also important to increase the accrual of young women with early BC in clinical trials focused on this important patient population.

299 INVITED

Strategies to preserve fertility in young breast cancer patients

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Abstract: Approximately 10% of all breast cancers appeared in women under 39 years. Improved treatment of breast cancer in premenopausal patients increased survival rates, but the therapy may influence fertility and ovarian function. Currently there is a big public and individual interest of breast cancer affected women in preservation of ovarian function and fertility. Chemotherapy induced amenorrhea (CIA) has many objective (osteoporosis, cardiovascular, urogenital atrophy, cognitive etc.) and subjective (hot flushes, sleep disturbances, change of mood etc.) consequences. In patients with breast cancer who wish to avoid a CIA and to preserve their fertility ovarian protection by GnRH agonists, cryopreservation of operative sampled ovarian tissue or obtained fertilized or non-fertilized eggs after stimulation and puncture or embryos after in vitro fertilization are technically possible. However there are no evidence-based recommendations for preservation of fertility or ovarian function in breast cancer patients. Except the cryopreservation of embryos all other procedures are experimental. It is also undefined who is going to carry the costs. Moreover, there are recent data that the reappearance of ovarian hormones may stimulate occult tumor cells in hormone sensitive breast cancer. Therefore it seems necessary to inform breast cancer patients about the possible negative effects of preservation of ovarian function.

300 INVITED

Child-bearing in breast cancer survivors

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Over the last decades time of childbearing has been steadily postponed in the western world. Therefore, an increasing number of women are seeking medical advice concerning pregnancy after treatment of breast cancer. Since oestrogen is an established growth factor in breast cancer, it has been discussed whether women should be advised against pregnancy subsequent to breast cancer treatment because of the fear of a negative prognostic effect of the high oestrogen levels associated with pregnancy.
The literature on the subject has been sparse, and the majority of the studies is small and methodological insufficient. Lately some harder evidence has appeared indicating that pregnancy after breast cancer treatment does not worsen prognosis. In the latest update on material from Danish Breast Cancer Coopertive Group, DBCG, 371 women experienced pregnancy after treatment of breast cancer (1). In a multivariate analysis that included age at diagnosis, stage of disease, and pregnancy history prior to diagnosis, women who had a full-term pregnancy subsequent to breast cancer treatment were found to have a reduced risk of dying (relative risk: 0.73; 95% confidence interval: 0.54−0.99) compared with other women with breast cancer. The effect was not significantly modified by age at diagnosis, tumour size, nodal status, or pregnancy history before diagnosis of breast cancer. Furthermore, neither spontaneous abortions nor induced abortions subsequent to breast cancer treatment seem to influence the prognosis. Overall, the fertility rate is reduced to one third, and the incidence of induced abortion is significantly increased among women treated for breast cancer.
Breast cancer is potential life-threatening disease, but many women do get cured. On the basis of the present knowledge women believed to be cured from breast cancer should not be advised from getting pregnant.

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Scientific Symposium (Thu, 24 Sep, 09:00−11:00)
New directions in the treatment of gastric cancer

301 INVITED

Changing epidemiology of gastric cancer – influence on treatment strategies and outcome

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In spite of the decreasing trend worldwide, gastric cancer is still the 4th most common malignancy in incidence and the 2nd most common cause of cancer death. The most remarkable change in gastric cancer epidemiology in recent decades is shift of the primary tumor location from distal to proximal, which was the most dramatic in Western countries like Europe and US. So, the incidence of lower esophageal (EA) and esophagogastric junction adenocarcinoma (EGJA) has increased rapidly in Western countries, while the incidence of gastric non-cardiac adenocarcinoma (GA) has decreased. This shift of primary tumor site can be attributed to several factors; increasing gastroesophageal reflux disease related to obesity, decreased H. pylori infection, and increased consumption of fresh fruits and vegetables with decreased consumption of salt or salted foods. In contrast, such a change has not been so apparent in East Asian countries like Korea and Japan. There is a minimal tendency of decreasing incidence of gastric cancer in this region as well. But, the incidence of gastric cancer is still very high and no change is noticed in the incidence of EA and EGJA. Because of this change in epidemiology of gastric cancer worldwide, issues have been raised for the proper management of gastric cancer.
Among the issues, the most critical question would be 'could EA and/or EGJA be managed in the same principle as GA?' In etiology, EA is known to be associated with gastroesophageal reflux, while GA develops associated with H. pylori infection. EA also shows different clinical behavior from GA. Because of lack of serosal envelope and the rich submucosal lymphatic network, esophageal cancer can easily develop extensive local infiltration and lymph node involvement. So, the TNM staging classification for GA cannot be applied to EA. For localized tumors, treatment of EA is different from GA. Esophagectomy, either transthoracic or transhiatal, is necessary for EA, but not for GA. Since EGJA develops between esophagus and stomach, both staging systems for EA and GA have been used for EGJA. But, recent studies suggest that EGJA is etiologically and clinically closer to EA than GA. For metastatic or recurrent tumors, systemic chemotherapy is indicated in both EA and GA. Chemotherapeutic agents active for both EA and GA were not so different. So, in many UK clinical trials of systemic chemotherapy for GA mostly include EA as well as EGJA. And, inclusion of two tumor types different in etiology and biology in a clinical trial was justified with a recent UK study showing no difference in outcome with conventional cytotoxic chemotherapy among EA, EGJA, and GA. But, recent studies of targeted agents suggest that there may be difference in response to targeted agents among these tumors. For instance, Dragovich et al. reported that erlotinib was active in EGJA, but inactive in GA. Recent ToGA study also suggested that efficacy of HER2 targeting therapy would not be the same between EGJA and GA because HER2 overexpression was more frequently found in EGJA than in GA. These indicate that EA would be better treated separately from GA or EGJA. And, for the global phase III trials of cytotoxic or targeted therapy on gastric cancer, either location of the primary gastric tumor (EGJA vs GA) or geographical region (Western vs East Asia) should be included in stratification factors for randomization.

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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