In the Dutch Gastric Cancer Group trial 711 patients that were treated with curative intent were randomized between D1 and D2 lymph node dissection. After a median follow up of 11 years there was no survival difference (30% vs. 35%; $p = 0.53$). Morbidity (25% vs. 43%; $p < 0.001$) and mortality (4% vs. 10%; $p = 0.004$) however, were significantly higher in the D2 group [4]. In the British MRC trial 400 gastric cancer patients were also prospectively randomized between D1 and D2 lymph node dissection [5]. Five year survival was 35% in the D1 and 33% in the D2 group; morbidity was 28% and 46% respectively, mortality was 6.5% for D1 and 13% in D2. Since these two trials were published a lot of debate has been generated about two topics. First of all, since subgroup analyses have indicated a trend for better survival in N2 patients after a D2 dissection, the question has risen whether there is a role for D2 resections in this subset of patients. Furthermore, there is considerable debate about the role of routine splenectomy and resection of the pancreatic tail in order to facilitate a D2 resection. It is hypothesized that in performing a D1 dissection without splenectomy and resection of the pancreatic tail, together with dissection of at least 15 (N1 and N2) nodes, a so-called D1 over (D1+) resection, can result in better outcome [6,7].

In 2005 final results of the MAGIC-study on perioperative chemotherapy have been presented [8]. In this large multicenter study patients were randomized between surgery only and 3 cycles preoperative ECF (epirubicin, cisplatin, 5-FU) followed by surgery and then 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). It should be noted that 80% underwent surgical resection, and that 66% of the patients commenced the postoperative chemotherapy and 42% completed the entire treatment. In addition, 50% of patients who completed preoperative chemotherapy and surgery, also completed postoperative treatment. The main reason (70% of the patients) for not starting postoperative chemotherapy was disease progression or patient choice (Cunningham, ASCO GI 2006). Despite this disappointing number of patients undergoing systemic treatment, perioperative chemotherapy with ECF may be considered as a new standard of treatment in operable gastric cancer.

In a Cochrane review of randomized trials in advanced gastric cancer highest survival rates were achieved with anthracyclines, cisplatin and 5-FU, both independently and in combination (Cochrane Library, 2005). Within these combinations ECF proved to be tolerated best. However, the use of continuous infusional 5-FU is considered cumbersome, because it requires the implantation of central venous catheter devices and the use of portable infusion pumps, which are associated with complications such as thrombosis and wound infection. Capecitabine, a prodrug and oral analogue of 5-FU, is believed to mimic continuous infusion of 5-FU and has demonstrated to be at least equally effective in tumor control and to be less toxic than intravenous 5-FU in patients with stage III and IV colon cancer.

In 2001, with the introduction of postoperative combined chemoradiotherapy for the first time a substantial improvement in survival and locoregional control has been described. In the SWOG/ Intergroup 0116 trial 556 patients were prospectively randomized between surgery only and surgery plus postoperative chemoradiotherapy. Radiotherapy consisted of 45 Gy in 25 fractions in five weeks. The chemotherapy regimen consisted of three cycles of 5-fluorouracil and leucovorin according to the Mayo regimen perioperatively and two shortened courses during radiotherapy. An impressive increase in median overall survival was obtained in the chemoradiotherapy group; 36 months versus 27 months in the surgery only group. Furthermore relapse free survival was prolonged from 19 months in the surgery only arm to 30 months in the chemoradiotherapy arm. It was thus shown that in gastric cancer too, the advantage in combining modalities is the ability to address both locoregional and systemic disease simultaneously. This postoperative chemoradiotherapy regimen has become standard treatment in the USA; 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 the abovementioned pivotal MAGIC and SWOG/Intergroup studies together, the important question that needs to be answered is whether postoperative chemoradiotherapy improves survival and/or locoregional control in patients that receive neoadjuvant chemotherapy followed by a D1+ gastric resection. We therefore conduct a prospective randomized multicenter phase III trial addressing this important question. To ascertain patient compliance and improve patient selection/ treatment tailoring, we plan to incorporate validated prognostic and predictive tests, such as Maruyama Index and nomogram for gastric cancer. In the chemoradiotherapy arm state-of-the-art 3D-conformal or Intensity-Modulated RadioTherapy (IMRT) should be a minimal requirement in order to limit normal tissue toxicity, in particular kidney damage. The chemotherapy schedule in both arms should be effective and safe. The combination of epirubicin, cisplatin and capecitabine fulfils these requirements. An optimized chemoradiotherapy schedule with radiosensitizing drugs during the entire radiotherapy treatment has been established with daily cisplatin and capecitabine in our phase I−II study.

- A phase III study which randomizes between preoperative chemotherapy (3 courses of epirubicin, cisplatin and capecitabine (ECC)) and D1+ gastric surgery followed by postoperative chemotherapy (another 3 courses of ECC) or chemoradiotherapy. Chemoradiotherapy consists of 45 Gy radiotherapy in 25 fractions with concurrent capecitabine and cisplatin (protocol available upon request).

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Special session (Wed, 26 Sep, 13:30−14:30)
New developments in clinical functional imaging

139 INVITED

Angiogenesis imaging

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Background: Angiogenesis, the growth of new blood vessels, plays an important role in reproduction and wound healing as well as in tumor progression. Non invasive imaging of angiogenesis can help in preclinical drug discovery and development and can also provide biomarkers during clinical monitoring of targeted antiangiogenic therapy.
Materials and Methods: Over the last years multiple approaches for imaging angiogenesis were developed for the various imaging modalities, providing structural, functional and molecular markers of the process.
Results: Imaging angiogenesis includes nowadays a large family of methods providing structural information on blood volume, vessel diameter and tortuosity. Functional information revealed by imaging includes blood flow and perfusion, vessel permeability and vasoreactivity. Lastly molecular imaging allows to probe changes in the composition and enzymatic activity in the extracellular matrix, expression of specific cell surface markers on endothelial cells, and imaging methods for following the recruitment of vascular and perivascular precursor cells as well as in vivo detection of gene expression.
Conclusions: Over the last decade multiple imaging approaches were developed to detect angiogenesis, thus complementing the efforts for therapeuric intervention. Clinical translation of these imaging approached could help tailor antiangiogenic therapy and provide early mechanism based markers for response.

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Two-photon imaging of tumour invasion

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Multiphoton microscopy has defined standards for 3D fluorescence and higher harmonic generation analysis of cells and tissue structures in vitro and in vivo. Compared to single-photon excited confocal microscopy, two-photon microscopy utilizes near-infrared (NIR) excitation generating twice to multi-fold enhanced tissue penetration, reduced light scattering and