**6503** ORAL

**Centralization for Esophagectomy but Not for Gastrectomy in the Netherlands, the Relation Between Annual Hospital Volume, Postoperative Mortality and Long Term Survival**

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**Background:** High hospital volume is associated with better outcomes in both esophageal and gastric cancer surgery. In the Netherlands, a minimal volume standard of 10 procedures a year has been introduced for esophagectomies in 2006. For gastric cancer, no minimal volume standard was set. Aims of this study are to describe changes in annual hospital volumes, mortality and long term survival for esophageal and gastric cancer, and to explore if high hospital volume is associated with lower postoperative mortality and better long term survival in the Netherlands.
**Material and Methods:** From 1989–2009, 24,246 patients underwent surgery for non-metastatic esophageal (N = 10,025) or gastric cancer (N = 14,221) in the Netherlands. Hospital volumes were defined as low (1−10/yr), medium (11−20/yr), and high (>20/yr) for esophagectomy, and for gastrectomy as low (1−5/yr), medium (6−10/yr), and high (>10/yr). Relations between hospital volume and outcomes were analyzed using Cox regression, correcting for case-mix and use of multi-modality treatment.
**Results:** From 1989–2009, the proportion of patients treated in high-volume hospitals increased from 7% to 64% for esophageal cancer, but decreased from 53% to 23% for gastric cancer (both $P < 0.001$). In the study period, six-month mortality decreased from 15% to 7% after esophagectomy, and from 18% to 13% after gastrectomy. Three-year survival increased after esophagectomy (33% to 47%), and to a lesser extent after gastrectomy (44% to 49%). After case-mix adjustments, high hospital volume was associated with lower 6-month mortality (HR 0.47, $P < 0.001$), improved 3-year survival (HR 0.74, $P < 0.001$) and increased lymph node yield (RR 1.7, $P < 0.001$) after esophagectomy, but not after gastrectomy.
**Conclusions:** Centralization of esophagectomy was effectively implemented in the Netherlands, which resulted in lower mortality, improved survival and higher lymph node yields. Gastric surgery is mainly performed in low and medium volumes, and mortality and survival for gastric cancer improved to a lesser extent. The marked difference between outcomes after esophagectomy and gastrectomy indicates an urgent need for improvement in quality of surgery and perioperative care for gastric cancer in the Netherlands.

**6504** ORAL

**Safety and Efficacy of Epirubicin, Cisplatin, and Capecitabine (ECX) Plus Rilotumumab (R) as First-line Treatment for Unresectable Locally Advanced (LA) or Metastatic (M) Gastric or Esophagogastric Junction (EGJ) Adenocarcinoma**

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**Background:** R is an investigational, fully human monoclonal antibody to hepatocyte growth factor (HGF) that prevents HGF from binding to the c-Met receptor. This 3-arm, placebo (pbo)-controlled, randomized, double-blind, multi-center, phase 2 study (sponsor: Amgen Inc.; ClinicalTrials.gov ID: NCT00719550) estimated the effect of adding R to ECX on PFS in patients (pts) with gastric cancer.
**Materials and Methods:** Eligibility: unresectable LA or M gastric or EGJ adenocarcinoma; ECOG PS 0 or 1; adequate organ function; no previous systemic therapy for advanced gastric cancer; written informed consent. Regulatory and Institutional Review Board approvals were obtained. Randomization was 1:1:1 to ECX (50 mg/m$^2$ IV day 1, 60 mg/m$^2$ IV day 1, 625 mg/m$^2$ BID orally days 1−21, respectively) + R 15 mg/kg IV Q3W (Arm A); ECX + R 7.5 mg/kg IV Q3W (Arm B); or ECX + pbo (Arm C). Stratification factors: LA vs M disease and ECOG PS 0 vs 1. Primary endpoint: progression-free survival (PFS) by investigator assessment. Secondary endpoints: overall survival (OS), objective response rate, and safety.
**Results:** 121 pts were randomized between 19 October 2009 and 23 June 2010 (Arms A/B/C: 40/42/39). Disease characteristics: gastric, 83/79/79%; EGJ, 18/12/10%; distal esophageal, 0/10/10%; M, 88/90/87%; LA, 13/10/13%. Median number of cycles administered on Arms A/B was 5. Most common reasons for discontinuation of R or pbo were adverse events (AE) in Arm A/B vs C (25/29 vs 8%) and disease progression in Arm C (25/19 vs 54%). See table for efficacy. All grade AEs with a >10% difference between Arms A and B vs C: neutropenia, 54/33%; alopecia, 41/26%; anemia,40/28%; decreased appetite, 28/15%; peripheral edema, 27/8%; thrombocytopenia, 11/0%. Grade 3/4 AEs ⩾10% pts in any arm, Arms A/B/C: neutropenia, 44/45/28%; anemia, 15/12/13%; fatigue 8/19/15%; pulmonary embolism, 8/10/10%; vomiting, 10/7/10%; hand foot syndrome, 8/10/5%; deep vein thrombosis, 5/10/0%. Grade 5 events: hematemesis, peritonitis, septic shock, intracranial hemorrhage (1 each Arm A); hematemesis, fall (1 each Arm B); syncope, cardiac arrest (1 each Arm C).
**Conclusions:** Addition of R to ECX appeared to improve PFS (HR = 0.58), which was more pronounced with R 7.5 mg/kg vs R 15 mg/kg. A higher incidence of peripheral edema, hematologic toxicities, and thromboembolic events were seen with the combination of R and ECX. OS and biomarker data will be presented.

| | Arm A n = 40 | Arm B n = 42 | ArmA+B n = 82 | Arm C n = 39 | Arm A vs C | Arm B vs C | Arm A+B vs C |
|---|---|---|---|---|---|---|---|
| PFS events, n (%) | 27 (68) | 28 (67) | 55 (67) | 32 (82) | | | |
| Median PFS (80% CI), months | 5.3 (4.1−5.7) | 6.3 (4.5-7.0) | 5.6 (4.6-6.8) | 4.2 (3.7−4.6) | HR = 0.70 (0.49–1.02) | HR = 0.49 (0.34–0.70) | HR = 0.58 (0.43–0.79) |
| Pts evaluable for tumour response, n | 36 | 40 | 76 | 38 | | | |
| Objective response rate, n (%) | 10 (28) | 18 (45) | 28 (37) | 9 (24) | P = 0.79 | P = 0.06 | P = 0.20 |

HRs were adjusted for stratification factors.

**6505** ORAL

**Update of AMC 0101 Study − a Randomized Phase III Trial of Intraperitoneal Cisplatin and Early Mitomycin-C Plus Long-term Doxifluridine Plus Cisplatin (iceMFP) Versus Mitomycin-C Plus Short-Term Doxifluridine (Mf) as Postoperative Adjuvant Chemotherapy for Grossly Serosa-positive Advanced Gastric Cancer (NCT00296322)**

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**Background:** To improve the postoperative adjuvant chemotherapy in serosa-involving AGC, we have adopted the strategies of intraperitoneal and early start of chemotherapy, as well as prolongation of oral fluoropyrimidine and addition of cisplatin (P) to Mf regimen. This phase III trial was designed to determine whether experimental iceMFP could improve 3 year relapse free survival rate (3yRFSR) compared to control Mf. (For HR 0.66, $\alpha = 0.05$, $\beta = 0.2$, N = 527 with 192 events.) Three year follow-up results were reported in 2008 ASCO meeting. Here we report long-term follow-up results for confirmation.
**Methods:** Pts whose tumour were grossly seroa-positive and able to be resected curatively were randomized during operation to receive either Mf or iceMFP. Pts with postoperative pathologic stage I or IV (M1) were excluded after surgery. For Mf, 20 mg/m$^2$ of mitomycin-C (M) was injected 3−6 wks after surgery and 4 wks later, 460–600 mg/m$^2$/day of doxifluridine was administered orally for 3 months. For iceMFP, 100 mg of P in 1 L of saline was administered intraperitoneally for 2 h during surgery and 15 mg/m$^2$ of M was injected 1 day after surgery. Doxifluridine was started 4 wks after surgery and extended for a total of 12 months and 6 shots of monthly 60 mg/m$^2$ of P were added.
**Results:** Between Oct 2001 and Apr 2007, a total of 640 pts were randomized (318 in Mf, 322 in iceMFP). One hundred and nineteen pts (60

in Mf, 59 in iceMFP) were excluded because of postoperative stage I in 90, IV (M1) in 13, positive resection margin in 10, and others in 6. Therefore, a total of 521 pts (258 in Mf, 263 in iceMFP) were eligible for intent-to-treat analysis. Postoperative stages were II in 33.4%, IIIA in 31.9%, IIIB in 17.5%, and IV in 17.3% of pts. With a median follow-up of 6.6 years, a total of 271 events (relapse or death) have been observed. As compared with Mf group, iceMFP group had a higher likelihood of relapse free survival (RFS) (HR, 0.73; 95% C.I. 0.57–0.93; p = 0.0092; 5yRFSR 53.9% vs 46.3%) and of overall survival (OS) (HR, 0.77; 95% C.I. 0.60–0.98; p = 0.0365; 5yOSR 59.2% vs 50.3%).
**Conclusions:** Considering no benefit of adding cisplatin and prolongation of oral doxifluridine to Mf chemotherapy in curatively resected AGC pts (AMC0201), intraperitoneal cisplatin and/or early start of chemotherapy seemed to be responsible for the improved efficacy of iceMFP chemotherapy in this study.

## *Poster Presentations* (Mon, 26 Sep, 09:30−12:00)
## Gastrointestinal Malignancies − Noncolorectal Cancer

**6506** POSTER

### Tricellulin Expression in Normal and Tumorous Human Pancreas

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**Background:** Tricellulin (TRIC) is the first identified member of transmembrane tight junction (TJ) proteins, found concentrated mainly at tricellular contacts. However, together with occludin and claudins it can also be detected at bicellular junctions. TJs play essential role in cell adhesion as well as in the maintenance of paracellular barrier and are also involved in signal transduction. Further, altered expression of several TJ components was observed during carcinogenesis and tumour progression. Previously, our group described significant differences between exocrine and endocrine pancreatic tumours related to claudin expression. The aim of the present study was to analyze the expression and localization of TRIC in normal human pancreas as well as in exocrine and endocrine primary tumours of the pancreas.
**Materials and Methods:** A total of 82 cases were studied: 20 normal pancreas, 44 ductal adenocarcinomas (PDACs) (grade 1−3), 15 endocrine neoplasms (PENs) and 3 acinar cell carcinomas (ACCs). Fluorescent microscopic examination and Western-blot analysis were performed on fresh frozen samples, immunohistochemical analysis and RT-PCR on formalin-fixed, paraffin embedded materials. Data were analyzed by digital morphometry and evaluated statistically.
**Results:** TRIC was found apically localized in normal ducts and acini. Intensive, spotty immunopositivity was detected at tricellular contacts, while weaker signals were observed between two cells. Langerhans islets were negative. The appearance of TRIC in PDACs, however, was unorganized as compared with normal tissue. Well differentiated PDACs expressed TRIC at significantly higher levels compared with poorly differentiated adenocarcinomas. Kaplan-Meyer analysis showed significant correlation between survival and differentiation of PDACs and inverse correlation with TRIC expression. ACCs expressed TRIC in atypical, abortive acinar cells. All PENs were TRIC negative.
**In conclusion**, this is the first report to describe the TRIC expression profile in normal and neoplastic human pancreas. Both normal and tumorous pancreatic exocrine tissues expressed TRIC, whereas no expression was notable in the normal and tumorous endocrine cells. Further, TRIC expression in PDACs revealed significant negative correlation with the degree of differentiation and survival.
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**6507** POSTER

### Effects of the Proteasome Inhibitor Bortezomib Alone and in Combination With Chemotherapeutic Agents in Gastric Cancer Cell Lines

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The proteasome plays a pivotal role in controlling cell proliferation, apoptosis, and differentiation in a variety of tumour cells. Bortezomib is a boronic acid dipeptide derivative, which is a selective and potent inhibitor of the proteasome and has prominent effects in vitro and in vivo against several solid tumours. We examined the anti-proliferative and apoptotic effects of bortezomib in three gastric cancer cell lines (SNU638, MUGC-3 and MKN-28), along with its antitumour combination effects with other chemotherapeutic agents.
Tumour cell growth inhibition and apoptosis was measured by MTT assay and FACS analysis, respectively. Apoptosis- and cell cycle-associated protein expression levels were measured by Western blot assay. Bortezomib induced the suppression of tumour cell growth and apoptosis in a dose-dependent manner with an inhibitory dose (ID)50 of approximately 0.5 μg/ml in all gastric cancer cell lines tested. Further combination treatment with cisplatin and docetaxel, in particular with docetaxel displayed dramatically increased tumour cell growth suppression in all three gastric cancer cell lines, as compared to single drug treatment alone. This was concomitant with the induction patterns of apoptotic cells. Bortezomib treatment increased the Bax protein expression. Moreover, combination treatment of bortezomib plus docetaxel resulted in a dramatic increase in the Bax expression. In contrast, Bcl-2 expression was decreased by combination treatment with bortezomib plus docetaxel in SNU638 cells. Finally, bortezomib, docetaxel and to a greater degree bortezomib plus docetaxel increased the expression levels of p27 proteins even without influencing p53 expression levels. Bortezomib has profound effects on tumour cell growth inhibition and induction of apoptosis in human gastric cancer cells, suggesting that bortezomib may be an effective therapeutic drug for patients with gastric cancer. Further combination studies with other chemotherapeutic drugs, in particular docetaxel showing more tumour cell growth inhibition and apoptosis suggest that combining bortezomib with docetaxel might be more effective for displaying tumour cell growth inhibitory effects in gastric cancer cells through regulation of Bcl-2, Bax and p27 proteins in vitro.

**6508** POSTER

### A Case–control Study on the Effect of Apolipoprotein E Genotype on Gastric Cancer Risk and Progression

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**Background:** Apolipoprotein E (ApoE) is a multifunctional protein playing a key role in the metabolism of cholesterol and triglycerides as it mediates blood clearance of cholesterol-rich particles. ApoE gene (19q13.2) has three major isoforms encoded by ε2, ε3 and ε4 alleles with the ε4 allele associated with hypercholesterolemia and the ε2 allele with the opposite effect. An inverse relationship between cholesterol levels and gastric cancer (GC) has been previously reported, although the relationship between ApoE genotypes and GC has not been explored to date.
Since the question on the role of hypocholesterolemia as a predisposing factor, or result of the preclinical stage of GC itself, remains still under debate, our hospital-based case-control study aimed to overcome this issue by directly looking at the relationship between ApoE genotypes and GC, as well as the interaction with potential effect modifiers.
**Materials and Methods:** One hundred and fifty-six gastric cancer cases and 444 hospital controls were genotyped for *apoE* polymorphism. The relationship between GC and putative risk factors was measured using the adjusted odds ratios (ORs) and their 95% confidence intervals (CIs) from logistic regression analysis. A gene-environment interaction analysis was performed.

Table: Distribution of *ApoE* polymorphism among gastric cancer cases and controls

| | Cases n (%) | Controls n (%) | OR (95% CI)[†] |
|---|---|---|---|
| ε3/ε3 | 109 (71.71) | 253 (62.94) | 1* |
| ε3/ε2 or ε2/ε2 | 15 (12.10) | 68 (21.18) | 0.40 (0.19–0.84) |
| ε3/ε4 or ε4/ε4 | 27 (19.85) | 76 (23.10) | 0.68 (0.36–1.26) |

[†]OR adjusted by age, gender, alcohol consumption (as continuous variable), packyears of smoking, grilled meat consumption and familiy history of gastric cancer. *Reference category.

**Results:** Alcohol consumption was associated with an increased GC risk with ORs of 1.84 (95% CI = 1.10–3.07) and 3.29 (95% CI = 1.36–7.98) for moderate and heavy drinkers, respectively. A nearly doubled GC risk (OR = 1.95, 95% CI: 1.06–3.60) was detected among individuals smoking more than 25 pack-years. As shown in the table, a statistically significant 60% decreased GC risk (OR = 0.40, 95% CI: 0.19–0.84) was observed for those carrying at least one *apoE* ε2 allele if compared with