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

J.L. Dikken[1], A.E. Dassen[2], V.E.P. Lemmens[3], L. van der Geest[4], K. Bosscha[2], M. Verheij[5], C.J.H. van de Velde[6], M.W.J.M. Wouters[7]. *[1]Leiden University Medical Center, Surgical Oncology, Leiden, The Netherlands; [2]Jeroen Bosch Ziekenhuis, Surgery, Den Bosch, The Netherlands; [3]Comprehensive Cancer Center, South, Eindhoven, The Netherlands; [4]Comprehensive Cancer Center, The Netherlands, Leiden, The Netherlands; [5]The Netherlands Cancer Institute − Antoni van Leeuwenhoek Hospital, Radiotherapy, Amsterdam, The Netherlands; [6]Leiden University Medical Center, Surgery, Leiden, The Netherlands; [7]The Netherlands Cancer Institute − Antoni van Leeuwenhoek Hospital, Surgery, Amsterdam, The Netherlands*

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.

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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

T. Iveson[1], R.C. Donehower[2], I. Davidenko[3], S. Tjulandin[4], A. Deptala[5], M. Harrison[6], E. Loh[7], Y. Jiang[8], K. Oliner[9], S. Dubey[7]. *[1]Southampton University Hospitals Nhs Trust, Medical Oncology, Southampton, United Kingdom; [2]John Hopkins Medical Center, Medical Oncology, Baltimore, USA; [3]State Institution of Public Health, Regional Clinical Oncology Dispensary, Krasnodar, Russian Federation; [4]Russian Cancer Research Center, Clinical Pharmacology and Chemotherapy, Moscow, Russian Federation; [5]Centralny Szpital Kliniczny Ministerstwa Spraw Wewnetrznych, Administracji Klinika Onkologii i Hematologii, Warszawa, Poland; [6]Mount Vernon Hospital, Mount Vernon Cancer Centre, Northwood, United Kingdom; [7]Amgen Inc., Oncology, So. San Francisco, USA; [8]Amgen Inc., Biostatistics, Thousand Oaks, USA; [9]Amgen Inc., Molecular Sciences and Computational Biology, Thousand Oaks, USA*

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.

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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)

Y.K. Kang[1], M.H. Ryu[1], H.M. Chang[1], D.Y. Zang[2], T.W. Kim[1], D.H. Yang[3], S.J. Jang[4], J.H. Yook[5], S.T. Oh[5], B.S. Kim[5]. *[1]Asan Medical Center, Department of Oncology, Seoul, Korea; [2]Hallym University Medical Center, Division of Hematology-Oncology, Anyang, Korea; [3]Hallym University Medical Center, Department of Surgery, Anyang, Korea; [4]Asan Medical Center, Department of Pathology, Seoul, Korea; [5]Asan Medical Center, Department of Surgery, Seoul, Korea*

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