**6561** POSTER

**Concurrent chemoradiotherapy with weekly docetaxel and cisplatin in advanced esophageal cancer**

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**Background:** How best to manage advanced esophageal cancer remains unresolved, especially in palliative care. To improve the symptoms, such as dysphaghia, concurrent chemoradiotherapy has been useful treatment option in advanced esophageal cancer. Recently, docetaxel has been widely used in esophageal cancer. Therefore this study was performed to determine the feasibility and safety of concurrent chemoradiotherapy with weekly docetaxel and cisplatin in advanced esophageal cancer.
**Methods:** Patients with locally advanced or metastatic esophageal squamous cell carcinoma, who have adequate organ function were eligible. During chemoradiotherapy, docetaxel and cisplatin were given at a dose of 20 mg/m$^2$ and 25 mg/m$^2$, respectively at D1, D8, D15. The cycle of this treatment was 28 days. 2 cycles of chemotherapy was done during radiotherapy. Radiotherapy was started at a dose of 200 cGy/day, up to a total of 5400 cGy.
**Results:** Twenty-one patients were enrolled and all of these patients were evaluable. The median age was 61.5 years (all male); ECOG performance status was 0/1/2 = 4/13/4; stage IIb/III/IVa/IVb = 3/8/3/7. Complete response was achieved in 6 patient (29%), partial response in 10 (47%), stable disease in 4 (19%), and one patients had progressive disease (5%). Therefore, the overall response rate was 97%. Over the grade 2 hematological toxicities, including of leucopenia, neutropenia, thrombocytopenia, had not seen during concurrent chemoradiotherapy. The most common non hematologic toxicity was odynophagia. Grade 3 or 4 of odynophagia has been developed in 5 patients (23.8%). One patient who showed PR had developed gastroesophageal fistula and inserted esophageal stent. Improvement of dysphagia after chemoradiotherapy had been shown in 9 patients among 17 patients (53%) who had complained of dysphagia at the time of diagnosis.
**Conclusions:** The concurrent chemoradiotherapy with weekly docetaxel and cisplatin was promising and safe in advanced esophageal cancer with results of good efficacy in tumor control, but also improvement of symptoms. This treatment would be helpful not only palliation, but also neoadjuvant setting.

**6562** POSTER

**Prognostic impact of number of lymph nodes examined and lymph node ratio among patients with gastric cancer**

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**Introduction:** Gastric cancer is still one of the leading cancers in incidence and mortality throughout the world. The only curative treatment is surgery with gastric resection and lymph node dissection. According to several guidelines a resection with at least 15 lymph nodes should be performed for proper staging and disease control. There is no consensus about the extent of lymph node dissection worldwide however.
In this perspective, we conducted a retrospective study in the Southern part of the Netherlands to evaluate the amount of lymph nodes examined and its relation to survival.
**Methods:** All patients resected for primary gastric cancer (M0-disease), diagnosed between 1999 and 2007 in the Dutch Southern Cancer Registry area were included (N = 880). The area includes 10 hospitals on 15 locations, which are served by 6 departments of pathology. The median number of lymph nodes was described by department of pathology, nodal status (N0 vs N+) and period of diagnosis (1999–2001 vs 2002–2003 vs 2004–2007). Follow-up of vital status was complete for patients diagnosed between 1999 and 2004. Differences in 5-year crude survival rates between node-negative patients with fewer than the total median number of nodes examined vs. patients with more nodes examined were analysed by means of a log-rank test. The ratio between the number of metastatic and evaluated lymph nodes was calculated, and divided into 4 groups: N-ratio 0 (0%), N-ratio 1 (0.1−19%), N-ratio 2 (20−29%), and N-ratio 3 ($\geqslant$30%).
**Results:** The median number of lymph nodes examined was 7; among patients with N0 disease 6, while among patients with N+ disease it was 8. Between 1999–2001 and 2004–2007, the median number of nodes examined increased from 6 to 8. The median number of nodes examined varied between the departments of pathology from 5 to 9. Among patients with N0 disease and <7 nodes examined, 5-year survival was 57% compared to 73% among patients with $\geqslant$7 nodes examined ($p = 0.01$). Using N-ratio, patients with N-ratio of 0% had higher 5-year survival rates (58%) compared to patients with a higher N-ratio (N-ratio 3: 5-year survival 11%, $p < 0.001$). Risk of dying was strongly correlated with N-ratio.
**Conclusion:** In our region insufficient number of lymph nodes are dissected and/or examined. The difference in lymph nodes examined between the departments of pathology could lead to differences in stage distribution and survival. N-ratio has a clear prognostic impact. Attempts to improve nodal assessment seem to be mandatory.

**6563** POSTER

**Phase I dose-finding study of sorafenib in combination with capecitabine and cisplatin as a first-line treatment in patients with advanced gastric cancer**

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**Background:** We conducted a phase I dose-finding study of sorafenib (S) in combination with capecitabine (X) and cisplatin (P) in patients with previously untreated metastatic or inoperable advanced gastric cancer.
**Methods:** Four dose levels of S, X, and P combination were tested. The doses of S (p.o. daily), X (p.o. on days 1−14), and P (i.v. on day 1) were escalated as following schedule; level 1: S 400 mg/d, X 1,600 mg/m$^2$/d, P 80 mg/m$^2$; level 2: S 800 mg/d, X 1,600 mg/m$^2$/d, P 80 mg/m$^2$; level 3: S 800 mg/d, X 2,000 mg/m$^2$/d, P 80 mg/m$^2$; level 1A: S 800 mg/d, X 1,600 mg/m$^2$/d, P 60 mg/m$^2$. The cycle was repeated every 3 weeks. Dose limiting toxicities (DLTs) were evaluated only in the first cycles. Standard 3+3 dose escalation design was implemented.
**Results:** Total 21 pts were enrolled in the study. No DLT was observed at dose level 1 (n = 3). One DLT (grade 3 diarrhea) was noted at dose level 2 (n = 6), and 2 DLTs (two grade 4 neutropenias longer than 5 days in duration) were observed at dose level 3 (n = 6), which made the level 3 as maximum tolerated dose (MTD). However, at cycle 2 and thereafter at dose level 2, the relative dose intensity (RDI) of S and X could not be maintained (mostly below 80%) due to the frequent dose reductions and cycle delays. So, we explored a new dose level (1A) between dose level 1 and 2. Since no DLT was found among 6 patients at level 1A with RDI mostly above 80% throughout the treatment period, level 1A was determined as recommended dose (RD). Most frequent grade 3 and 4 hematologic and non-hematologic toxicities were neutropenia (25.0% of cycles) and hand-foot syndrome (2.3% of cycles). The objective responses were confirmed in 10 out of 16 patients with measurable lesions (62.5%; 95% CI 38.8−86.2%). With a median follow-up of 12.7 months, estimated median progression-free survival and overall survival was 10.0 months (95% CI, 6.8−13.1 months) and 14.7 months (95% CI, 8.5−21.0 months), respectively.
**Conclusions:** Diarrhea and neutropenia were DLTs in this S, X, and P combination. The dose schedule of sorafenib 400 mg po bid daily with capecitabine 800 mg/m$^2$ po bid on days 1−14, and cisplatin 60 mg/m$^2$ iv on day 1 in every 3 weeks is recommended for further development in AGC.

**6564** POSTER

**Association of CYP2A6*4 with the efficacy of S-1 plus cisplatin in metastatic gastric cancer patients**

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**Background:** S-1, a novel oral fluoropyrimidine contains tegafur, which is converted to 5-fluorouracil mainly by *CYP2A6*. We evaluated the association between *CYP2A6* polymorphisms and treatment efficacy of S-1 plus cisplatin in metastatic gastric carcinoma (MGC) patients.
**Methods:** Chemonaive patients received S-1 40 mg/m$^2$ b.i.d. on days 1−14 and cisplatin 60 mg/m$^2$ on day 1 of a 3-week cycle. We analyzed the wild-type allele (*CYP2A6*1*) and four variant alleles that abolish of reduce enzyme activity (*CYP2A6*4, *7, *9* and **10*).
**Results:** Thirty-six MGC patients were enrolled. The frequencies of the *CYP2A6*4, CYP2A6*7, CYP2A6*9*, and *CYP2A6*10* alleles were 16.7%, 5.6%, 19.4%, and 2.8%, respectively. With a median follow-up duration of 32.3 months (range, 4.8−38.2 months), the median time to progression (TTP) was 4.4 months (95% CI, 3.1−5.7 months) and the median overall

survival (OS) was 12.0 months (95% CI, 8.1−15.9 months). Among the variant alleles, patient with *CYP2A6*4* had significantly inferior TTP than those without *CYP2A6*4* (median TTP, 3.7 vs. 4.8 months; $P = 0.04$) and tend to have inferior OS (median OS, 9.7 vs. 15.0 months; $P = 0.09$). Univariate analyses for age, sex, ECOG performance status (PS), tumor histology, and number of metastatic organ sites showed that ECOG PS was significantly associated with TTP (median TTP, 5.3 [PS 0/1] vs. 2.4 months [PS 2/3]; $P < 0.001$), as well as *CYP2A6*4*. In multivariate analysis, after adjusting for PS, the *CYP2A6*4* allele remained a statistically significant predector of TTP; patients with *CYP2A6*4* showed a 3.63-fold (95% CI, 1.54−8.55; $P = 0.003$) increased risk of progression compared to those without *CYP2A6*4*.

**Conclusion:** Our findings showed *CYP2A6*4* allele correlated with decreased treatment efficacy of S-1 plus cisplatin in previously untreated MGC patients.

**6565** POSTER

**The role of PET-TC in predicting the pCR in locally-advanced esophageal cancer (LAEC) after a preoperative CT-RT treatment: data from B152 trial**

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**Background:** the improvement of overall survival in pts with LAEC after a preoperative CRT treatment is correlated to the complete pathologic response (pRC). We aimed to examine the ability of PET-TC in predicting the complete pathologic response in LAEC pts enrolled in the B152 trial.
**Methods:** Eligibility criteria: resectable, locally advanced (uT3-T4 N0, any uT N1) squamous cell carcinoma (SCC) or adenocarcinoma (AC) of the esophagus; age 18−70 y; PS < 2; normal organ functions. All pts received induction treatment with 8 administration of Cetuximab (C) (400 mg/m$^2$ as starting dose followed by 250 mg/m$^2$/weekly) and 4 cycles of FOLFOX-4 every two weeks. In case of response pts underwent daily RT (180cGy fractions to 5040 cGy) with concurrent weekly C. At the end of treatment, pts without PD had esophagectomy. PET-TC was perfomed before starting treatment (time 0), after chemotherapy (time 1) and after radiotherapy (time 2). The purpose was to evaluate if there was a correlation between the metabolic response recorded by PET-TC on time 2 and the histopathological response on the surgical specimen.
**Results:** Up to April 2009, 42 pts, 32 men and 10 women, were enrolled from 4 institutions; among these pts, 6 were not evaluable (5 are still on therapy and 1 refused surgery). Among 36 pts evaluable, 22 pts were considered positive for residual disease at PET-TC evaluation and pathologic examination, 2 pts presented a pRC althought the PET-TC was positive, 5 pts resulted false negative (PET-TC negative but surgical specimen positive for disease), 7 pts were true negative (PET-TC negative with pRC obtained). Sensitivity to detect response was 81%, with a corresponding specificity of 77%. The positive and negative predictive values were 92% and 58%.
**Conclusions:** FDG-PET could be a valuable tool for the non invasive assessment of histopathologic tumor response after neoadjuvant radiotherapy and chemotherapy.

| Total of pts 36 (100%) | Residual disease pts (%) | pRC pts (%) |
|---|---|---|
| PET positive | 22 (61%) | 2 (6%) |
| PET negative | 5 (14%) | 7 (19%) |

**6566** POSTER

**A multicenter phase II study of induction CT with Folfox-4 and Cetuximab followed by RT and Cetuximab in locally advanced esophageal cancer (LAEC)**

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**Background:** Preoperative CRT improves the survival of pts with EC when compared with surgery alone. Epidermal growth factor receptor (EGFR) is overexpressed in 30−90% of EC and is associated with poor prognosis, providing the rationale for using the anti-EGFR monoclonal antibody Cetuximab (C). The purpose of the study was to investigate the efficacy, toxicity and feasibility of C with FOLFOX-4 regimen as induction CT followed by C and RT in pts with LAEC in a multicenter setting.
**Methods:** Eligibility criteria: resectable, locally advanced (uT3 or uN1, T4 if deemed resectable) squamous cell carcinoma (SCC) or adenocarcinoma (AC) of the esophagus; staged by EUS, CT and PET scan; age 18−70 y; PS < 2; normal organ functions. All pts received induction treatment with C at a starting dose of 400 mg/m$^2$ and further weekly infusion at a maintenance dose of 250 mg/m$^2$ and 4 cycles of FOLFOX-4 every two weeks. Post-induction EUS and CT scans were performed, while a PET scan was repeated early before second cycle of CT: pts without PD were given daily RT (180cGy fractions to 5040cGy) with concurrent weekly C. Post RT, EUS plus biopsies, CT scan and PET were performed. At wk 18, pts without PD had esophagectomy. A Simons two stage design was used. Primary endpoint was histopathological response rate.
**Results:** Up to January 2009, 42 pts, 32 men, were enrolled from 4 institutions; median age 59 y (35−70 y); AC 12; SCC 30; stage II 15, stage III 27 pts. At this time 39/42 pts were evaluable. The most frequent grade 3/4 toxicity of chemoradiotherapy were skin (32%), neutropenia (29%) and esophagitis (9%); 10 pts had no resection (9 progressive disease, 1 patient's refusal). Of 23 operated pts, 18 pts (77%) had RO-resection, 5 pts had palliative surgery. 2 pts died due to complications after surgery (1 after >30 days). The pathological response rate was 68%, with a complete histopathological remission recorded in 7 pts (38%);18 pts (42%) are still alive without residual or recurrent disease.
**Conclusions:** These results suggest the feasibility of incorporating Cetuximab into a preoperative regimen for LAEC pts and an encouraging antineoplastic activity with 68% histopathological responders.

**6567** POSTER

**Preoperative radiochemotherapy with cisplatin plus infusional high-dose 5-fluorouracil/leucovorin (LV5FU2) in locally-advanced esophageal carcinoma of UICC stages II and III – ongoing study**

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**Background:** Esophageal squamous cell carcinoma is a highly aggressive malignancy with a poor prognosis. Surgical resection has been the standard treatment for this cancer. Radical resection is limited because of the advanced stage of the disease at the time of diagnosis. Neoadjuvant radiochemotherapy has been proposed in this study on the basis that local down staging could increase the resectability rate in locally advanced carcinoma of the esophagus. Long term survival may be possible if the carcinoma of the esophagus respond to radiochemotherapy (CRT) and radical surgery is performed.
**Material and Methods:** This study is a part of Ministry of Science project number 145059 started in december 2006. Since than, 46 patients have been enrolled in this study: 6 females (13.04%) and 40 males (86.96%). Mean age was 56 y (range 37−74 y) According to UICC staging system 11 pts have been in clinical stage II (T3N0M0) and 35 pts in clinical stage III (T3N1M0, T4N0−1M0). Tumor location was as follows: cervical oesophagus 2 pts, upper third of thoracic oesophagus 21 pts, medium third 17 pts and lower third 6 pts. Preoperative radiotherapy with tumor dose of 45−50.4 Gy in 24−28 fractions have been applied with concomitant chemotherapy with Cisplatin plus infusion high/dose 5/fluorouracil/leucovorin (LV5FU2).