220 POSTER

Dose escalation with hyperfractionation and concurrent FP chemotherapy in inoperable esophageal cancer

J. Kim[1], J. Park[1], E. Choi[1], S. Ahn[1], S. Lee[1], S. Shin[1], S. Kim[2], S. Park[3], H. Song[4], H. Jung[5]. *[1] Asan Medical Center, Radiation Oncology, Seoul, Korea; [2] Asan Medical Center, Medical Oncology, Seoul, Korea; [3] Asan Medical Center, Thoracic Surgery, Seoul, Korea; [4] Asan Medical Center, Diagnostic Radiology, Seoul, Korea; [5] Asan Medical Center, Gastroenterology, Seoul, Korea*

Background: To evaluate the local control rates, survival rates, patterns of failure, and late complications for unresectable esophageal cancers which were treated with hyperfractionated concurrent chemo-radiotherapy with curative intent.

Material and methods: Eighty-five patients with unresectable esophageal cancers received radiation (6,000 cGy/50 fractions/5 weeks, with or without intraluminal brachytherapy with Ir-192, 9-12 Gy/3-4 fractions at 1 cm from the source) with concurrent chemotherapy (CDDP 60mg/m^2 on D1 and 29, 5FU 1,000 mg/m2 continuous infusion at D2-5, 30-33). Response to treatment was measured at 3 or 4 weeks after completion of radiation. Minimum and median follow-up period of surviving patients were 20 and 52 months, respectively.

Results: All patients successfully completed radiotherapy as prescribed. Seventy-five (88%) had reevaluation after treatment, and major responses rate was 73%, including 7 patients with complete remission. Minimal or no response were found in 18 (24%), and disease progression in 2 patients. Overall and disease free survival rates were 26.2% and 20.7% at 2 years and 15.5% and 14.8% at 5 years, respectively. When we compared the survival rates among the three groups, there was no significant difference; however, patients who received external beam dose of 60 Gy or higher showed improved disease free survival. Brachytherapy did not make any difference in disease free survival. Among the 65 whose failure sites could be identified, the rate of local recurrence or persistent local disease was 50.0% and distant metastasis was 29.3%. Hematologic toxicity of NCI-CTC grade 3 or higher was found in 15 patients (22.1%) during chemotherapy. Late esophageal complication was observed in 28 patients (32.9%) including 8 RTOG grade 3 or higher. But it was not related with brachytherapy (17/50 vs 13/35). Overall treatment related mortality rate was 4.7%.

Conclusion: With external beam dose of 60 Gy or higher, disease free survival rate was increased with simultaneous increase of esophageal complications. Hyperfractionation seemed to be not effective for decreasing late esophageal complications in this dose range.

221 POSTER

Modified capecitabine regimen for advanced/metastatic gastric cancer: Final results from a multicenter phase II trial

K. Kondo[1], K. Chin[2], J. Sakamoto[3], H. Kojima[4], M. Terashima[5], Y. Yamamura[6], T. Tsujinaka[7], I. Hyodo[8]. *[1] Nagoya National Hospital, Dept. of Surgery, Nagoya, Japan; [2] Cancer Institute Hospital, Dept. of Medical Oncology, Tokyo, Japan; [3] Kyoto University Graduate School of Medicine, Dept. of Epidemiological & Clinical Research Information Management, Kyoto, Japan; [4] Aichi Prefectural Hospital, Dept. of Gastroenterological Surgery, Okazaki, Japan; [5] Fukushima Medical University, Dept. of Sugery 1, Fukushima, Japan; [6] Aichi Cancer Center, Dept. of Gastroenterological Surgery, Nagoya, Japan; [7] Osaka National Hospital, Dept. of Surgery, Osaka, Japan; [8] National Shikoku Cancer Center, Dept. of Internal Medicine, Matsuyama, Japan*

Background: Capecitabine (Xeloda®) is a novel, orally administered, tumor-activated fluoropyrimidine carbamate with proven activity as first-line treatment in metastatic colorectal cancer. We performed an open-label, multicenter phase II study to evaluate the efficacy and safety of a modified Japanese capecitabine regimen in chemotherapy naïve patients with advanced/metastatic gastric cancer.

Methods: Patients with histologically documented gastric cancer were treated with capecitabine 828 mg/m^2 administered twice daily for 3 weeks followed by one week of rest. Treatment was repeated every 4 weeks for two or more cycles unless patients developed progressive disease. This 4-weekly intermittent regimen had been identified in a previous Japanese phase I study.

Results: A total of 60 patients were enrolled between Feb 1999 and Apr 2001. Baseline patient characteristics were as follows: male/female, 49/11; median age, 64 years (range 28-74); median treatment duration, 4 cycles (range 1-37). 55 patients were evaluable for response by an independent review committee. The overall response rate was 25.5% (95% CI, 14.7-39.0%), including 4 complete responses and 10 partial responses. A further 16 patients (29.1%) had stable disease. The median time to progression was 3.4 months (95% CI, 1.8-6.1 months) and median overall survival was 10.0 months (95% CI, 6.4-13.5 months). Hand foot syndrome, anorexia, nausea and diarrhea were the most common adverse events. The most frequent (greater than 10% of patients) grade 3/4 adverse event was hand foot syndrome (13.3%). However, no grade 3/4 diarrhea was observed and only 10% of patients developed grade 3/4 hematological toxicity.

Conclusion: This modified capecitabine regimen was convenient, effective, well tolerated and contributed to a long survival time when administered as first-line therapy in patients with advanced/metastatic gastric cancer. Further investigation of this capecitabine regimen as monotherapy and as part of combinations in the metastatic and adjuvant settings is warranted.

222 POSTER

Gastrazole, a novel CCKB/gastrin receptor antagonist, in the treatment of advanced pancreatic cancer: results from two randomised controlled trials

I. Chau[1], D. Cunningham[1], C. Russell[2], A.R. Norman[3], P. Harper[4], P. Harrison[5], P.J. Ross[1], R. Hull[6], M. Walker[6], J. Black[6]. *[1] Royal Marsden Hospital, Department of Medicine, London and Surrey, United Kingdom; [2] The Middlesex Hospital, Hepato-Pancreato-Biliary & Endocrine Surgical Unit, London, United Kingdom; [3] Royal Marsden Hospital, Department of Computing and Information, London and Surrey, United Kingdom; [4] Guy's Hospital, Department of Medical Oncology, London, United Kingdom; [5] King's College Hospital, Institute of Liver Studies, London, United Kingdom; [6] James Black Foundation, London, United Kingdom*

Background and purpose: Gastrin has been shown to be a growth stimulant in pancreatic cancer cells. Gastrazole is a potent and selective gastrin receptor antagonist. In a previous randomised controlled trial for advanced pancreatic cancer, protracted venous infusion (PVI) 5-FU produced 1-year survival rate of 23.5% (Maisey et al JCO 2002) – similar to that achieved with gemcitabine. Two randomised trials were conducted to assess the effect of gastrazole in advanced pancreatic cancer.

Patients and Methods: Patients with biopsy-proven, inoperable pancreatic carcinoma were recruited into both studies. Trial 9902 compared PVI gastrazole (500mg/day) with PVI placebo in a double blinded fashion. Trial 9901 compared PVI gastrazole (500mg/day) with PVI 5-FU (300mg/m2/day) in a single blinded fashion.

Results: Between June 00 and November 02, 18 patients (M:F 13:5) were randomised in trial 9902. The median age of patients was 60 (range: 44-78). 33% of patients had metastatic disease. Gastrazole produced significantly better survival compared to placebo (median 7.8 months vs, 4.5 months; 1-year survival: 38% vs. 11% respectively; log rank p=0.0167). No difference in toxicity was seen between gastrazole and placebo. Between June 99 and November 02, 98 patients (M:F 52:46) were randomised in trial 9901. The median age of patients was 65 (range: 35-82). 59% of patients had metastatic disease. No significant survival difference was detected between gastrazole and 5-FU (median: 3.6 months vs. 4.2 months; 1-year survival: 16.9% vs. 23.9% respectively; log rank p=0.7518). Toxicity of gastrazole was mild with significantly less diarrhoea (p=0.02), stomatitis (p

223 POSTER

Clinical results of proton radiation therapy alone for esophageal cancer

S. Sugahara[1], K. Tokuuye[1,2], T. Okumura[3], A. Nakahara[4], Y. Saida[5], K. Kagei[1,2], K. Ohara[1], S. Hata[1,2], N. Tanaka[4], Y. Akine[1,2]. *[1] Tsukuba University Hospital, Radiation Oncology, Tsukuba, Japan; [2] Tsukuba University, Proton Medical Research Center, Tsukuba, Japan; [3] Central Hospital and Cancer Center of Ibaraki Prefecture, Radiation Oncology, Tomobe, Japan; [4] Tsukuba University Hospital, Internal Medicine, Tsukuba, Japan; [5] Tsukuba University Hospital, Radiology, Tsukuba, Japan*

Background: Proton radiation therapy can deliver higher doses to the target with a considerably smaller dose affecting the adjacent normal tissue when compared to conventional radiotherapy. The aim of this study was to evaluate the clinical results of proton radiation therapy alone for patients with locally confined esophageal cancer.

Methods and Materials: Forty-six esophageal cancer patients who were treated with 250 MeV protons with or without x-rays between 1985 and 1998 were analyzed. All patients had local-regionally confined disease, and had squamous histology except for one adenocarcinoma. The median tumor length was 4.0 cm (range, 1.5-15.0). Forty patients received combinations of x-rays (median 48 Gy) and protons (median 31.7 Gy) over 44 - 99 days (median 61 days) as a boost. The median total dose of combined x-ray and

proton radiation for these patients was 76.0 Gy (range, 69.1-87.4 Gy). The remaining 6 patients received proton radiation therapy alone (75-89.5 Gy, median 82 Gy) over 33 - 72 days (median 55 days). The median follow-up period was 35 months (range, 4–138 months). We analyzed the tumor response, the survival rates, patterns of failure and morbidity.

Results: Thirty-nine (85%) patients showed a complete response within 4 months after completion of treatment. Five-year actuarial survival for the 46 patients, that for patients with clinical T1 (n=23), and that for those with clinical T2/3/4 (n=23) were 35.6%, 55.4%, and 16.3%, respectively. The five-year cause-specific survival for the 46 patients, that for patients with clinical T1, and that for clinical T2/3/4 were 69.8%, 95.2%, and 41.5%, respectively. The five-year local control rates for patients with T1 and T2/3/4 lesions were 82.9% and 32.4%, respectively. The sites of first treatment failures were local-regional for 16 patients and distant organs for 2 patients. Five patients (11%) developed grade 3 acute esophagitis according to the EORTC acute radiation morbidity scoring criteria. Late complications in the esophagus were grade 3 for 3 patients (7%) and grade 4 for 2 patients (4%) according to the EORTC late radiation morbidity scoring criteria.

Conclusions: The results suggest that proton radiation therapy is an effective modality for patients with locally confined esophageal cancer. Further studies are needed to determine the optimal total dose, fractionation schedules, and best combinations of protons and conventional x-rays.

224 POSTER

Docetaxel and cisplatin combination chemotherapy in patients with advanced or metastatic gastric cancer: results of a multicentre phase II study

J. Fahlke[1], K. Ridwelski[2], E. Kettner[3], U. Keilholz[4], C. Schmidt[1], K. Eichelmann[1], H. Lippert[1]. [1] *Otto-von-Guericke University, Dept. of Surgery, Magdeburg, Germany;* [2] *Städtisches Klinikum Dessau, Dessau, Germany;* [3] *Städtisches Klinikum Magdeburg, Magdeburg, Germany;* [4] *University hospital Benjamin-Franklin, Berlin, Germany*

Background: The aim of the present study was to evaluate the efficacy and tolerability of docetaxel and cisplatin in patients with advanced or metastatic gastric cancer.

Materials and methods: Metastatic disease was present in 85% of patients and 15% of patients had locally advanced gastric carcinoma. Eastern Cooperative Oncology Group performance status scores of 0, 1 or 2 were noted in 25%, 51% and 25% of patients, respectively. The median age was 59 years (range: 31-72 years). Patients received docetaxel 75 mg/m^2 and cisplatin 75 mg/m^2 on day 1 every 3 weeks for a maximum of 9 cycles.

Results: A total of 112 patients have been recruited. To date, toxicity, tumour response and survival data are available for 94 patients. The median number of cycles administered was 5 (range: 1-9). The overall response rate was 26.6% (complete remission: 4/94 (4.3%) patients, partial remission: 21/94 (22.3%) patients). A total of 34 (36.2%) patients showed disease stabilisation and cancer progression was seen in 27 (28.7%) patients. Tumour response was not evaluable in 8 (8.5%) patients. Haematological and nonhaematological toxicities were mild and occurred infrequently. World Health Organization defined grade 3 nausea/vomiting and peripheral neurotoxicity were observed in 12.6% and 6.1% of patients, respectively; grade 3-4 neutropenia was seen in 39.2% of patients; grade 3-4 infections, with or without neutropenia, occurred in 6.1% and 5.2% of patients, respectively. The estimated median survival was 9.7 months.

Conclusions: The combination of docetaxel and cisplatin was well tolerated and resulted in high tumour response rates in patients with gastric carcinoma. At present we are performing a phase III trial comparing the combination of docetaxel and cisplatin with the standard combination of cisplatin and 5-fluorouracil.

225 POSTER

Prognostic value of KIT mutation in localized gastrointestinal stromal tumors (GIST)

T.W. Kim[1], H. Lee[1], M.H. Ryu[1], M. Choe[2], J.S. Kim[2], H.M. Chang[1], J.H. Yook[3], B.S. Kim[3], J.S. Lee[1], Y.K. Kang[1]. [1] *Department of Oncology/Hematology,* [2] *Department of Diagnostic Pathology,* [3] *Department of Surgery, Asan Medical Center, Seoul, Republic of Korea*

Background: GIST is the most common mesenchymal tumor arising in the gastrointestinal tract. Recently, constitutional activation of *KIT* by mutation is shown to be a key pathogenetic mechanism in GIST. However, the prognostic significance of *KIT* mutation has not been defined yet.

Material and methods: The pathologic slides of primary mesenchymal tumors of the gastrointestinal tract experienced at the Asan Medical Center during the period of 1990-2001 were reviewed with immunohistochemical analysis with a panel of antibodies against CD117, CD34, desmin, SMA, and S100. After diagnosis of GIST was made, genomic DNA was extracted from formalin-fixed, paraffin embedded tumor tissues. PCR amplification and sequencing of the exon 9, 11, 13 and 17 were performed to detect *KIT* mutation. Clinical data of the cases were reviewed

Results: Total 91 cases of localized GIST was found to have curative resection between 1990 and 2001 and paraffin blocks were available for mutation analysis. The median age of the patient was 56(range:30-83). The stomach(57%) and small bowel(23%) were the most frequent primary sites. The median tumor size was 6 cm(range: 0.4-23). Exon 11 and 9 mutations were observed in 63 and 2 patients, respectively. However, no mutations were detectable in exon 13 and 17. Thus, *KIT* mutation rate was 71% in this patient population. The exon 11 mutations included in-frame deletions(38 cases), missense mutations(21 cases) and insertion or duplication(4 cases). Histologically, The cases with *KIT* mutation showed higher mitotic counts and more dense cellularity. For all 91 patients, the 5-year recurrence-free survival(RFS) and overall survival were 34% and 75%, respectively. The 5-year RFS for cases with *KIT* mutation were 23%, compared with the 75% for cases without *KIT* mutation(p=0.0028). Statistically significant RFS were also observed favoring mitotic counts of fewer than 5 mitoses/50 HPF, spindle-cell morphology, 5 cm or smaller tumors. Multivariate analysis with Cox 's proportional hazard model indicated that mitotic counts(≥5/50HFP; hazard ratio(HR)=6.1) and presence of *KIT* mutations(HR=10.6) were associated with recurrence.

Conclusion: The presence of *KIT* mutation as well as high mitotic count was an independent poor prognostic factor for the recurrence after curative resection of the localized GIST.

226 POSTER

Size and geometry of radiofrequency lesions: crucial knowledge to prevent local recurrence

S. Mulier[1], Y. Ni[2], Y. Miao[3], A. Rosière[1], A. Khoury[1], G. Marchal[2], L. Michel[1]. [1] *University Hospital Mont-Godinne, Dept. of Surgery, Yvoir, Belgium;* [2] *University Hospital Gasthuisberg, Dept. of Radiology, Leuven, Belgium;* [3] *The First Affiliated Hospital of Nanjing Medical University, Dept. of Surgery, Nanjing, China*

Background Radiofrequency (RF) coagulation of irresectable liver tumours has a local recurrence rate which varies among series but may be as high as 60%. We hypothesised that overestimation of expected coagulation size and a too ideal image of a perfect spherical geometry may have contributed in cases of failed local tumour control.

Material and methods: An exhaustive literature search (articles and abstracts) was carried out for the period from January 1st 1990 to December 31st 2002. The RF companies were asked to provide all available data. For each electrode and protocol, size and geometry of single-cycle thermal lesions were registered.

Results: No information at all on size and geometry was available for 17 of the 28 current commercial electrodes. Many descriptions of RF lesions are limited to the mean transverse diameter. With normal blood flow, diameter of lesions is often smaller than suggested by the length of the electrode tip or the diameter of the deployed prongs. Lesions are rarely perfect spheres but either ellipses or flattened spheres. Distortion of the RF lesion by nearby blood vessels is very common. Fusion of thermal zones between prongs of expandable electrodes can be incomplete. Blood flow interruption using a Pringle maneuver yields larger lesions that are less distorted and more complete.

Conclusion: Accurate knowledge of size and geometry of RF lesions is crucial to prevent local recurrence. For many electrodes that are currently used in patients, no or insufficient experimental data are available. RF companies are urged to produce and provide these data before releasing electrodes for patients' use on the market.