Poster presentations (Wed, 2 Nov)
GI – non-colorectal cancer

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Preliminary results of hypofractionated proton beam therapy for hepatocellular carcinoma

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Purpose/Objective: We have previously shown that proton beam therapy is effective and safe for patients with various conditions of hepatocellular carcinoma (HCC). The purpose of this study is to evaluate the efficacy and safety of hypofractionated proton beam therapy for HCC.
Materials/Methods: We treated patients having HCC with proton beam therapy to give 60 Gy in 10 fractions over 2 weeks when they met following criteria: patients had liver functions of Child-Pugh class A or B, had a solitary HCC less than 10 cm in maximal diameter and whose tumor was located more than 2 cm apart from the porta hepatis or digestive tract. Thirty-six out of 105 HCC patients, who were treated by proton beam therapy at University of Tsukuba from Sept. 2001 to Dec. 2003, met the criteria. The remaining 69 patients who were irradiated with other irradiation regimen such as 66 Gy in 22 fractions, 70 Gy in 35 fractions were excluded from this study. Of the 36 patients, 22 patients were men and 14 women. The median age was 66 years (26–85 years old). Twenty-six patients had Child-Pugh class A and 10 had B. The median tumor maximal diameter was 3 cm (0.8–9.3 cm). The patients were followed by CT or MRI every 3 months for 2 years after proton beam therapy and every 6 months after that. Two-year survival and local control rates were calculated from the beginning of proton beam therapy using the Kaplan-Meier method.
Results: The median observed period was 19 months (5–34 months). Thirty-one patients are alive and 5 dead at March 2005. The two-year survival rate was 70.3%. Local recurrence was observed in 2 patients at 16 and 18 months after the beginning of proton beam therapy, respectively. Two-year local control rate was 88.1%. Late complications of grade 2 or more were observed in 2 patients: one patient suffered from radiation pneumonitis (grade II) and rib fracture at 1 and 27 months after proton beam therapy; The other suffered from rib fracture at 8 months after proton beam therapy.
Conclusions: The irradiation regimen of a total dose of 60 Gy in 10 fractions appears effective and feasible for patients with HCC.

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Postoperative chemoradiotherapy in gastric cancer – results of two parallel phase I-II studies of a fixed radiotherapy regimen with escalating doses of cisplatin and capecitabine

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Background: The prospectively randomized Intergroup Study INT-0116 has demonstrated that postoperative 5FU-based chemoradiotherapy improves survival and locoregional control in gastric cancer. These results stimulated us to evaluate whether treatment outcome could be further improved using increasing doses of the radiosensitizing drugs cisplatin and capecitabine during radiotherapy.
Methods: Between December 2002 and May 2005, 70 patients with $T_{2-4}N_{0-3}M_0$adenocarcinoma of the stomach or distal esophagus were enrolled in two parallel running phase I-II studies. Treatment started in both studies within 60 days after surgery with capecitabine 1000 mg/m^2 bid on days 1–14. Thereafter radiation started to a total dose of 45 Gy in 25 fractions of 1.8 Gy to the original tumor site, anastomoses and adjacent lymph nodes on weekdays during weeks 4 through 8. In the first study capecitabine given concurrently with radiation was escalated in groups of 20 patients per dose level from 600 to 900 mg/m^2 bid (planned maximum 1000 mg/m^2 bid). In the second study, both cisplatin and capecitabine were given concurrently with radiation. Cisplatin was administered in an escalating daily dose of 3 to 6 mg/m^2 (iv) and capecitabine was escalated from 250 to 650 mg/m^2 bid in groups of at least 3 patients per dose level.
Results: Up to May 2005, 47 patients have completed treatment with capecitabine only; one withdrew early due to anxiety. The full radiation and capecitabine dose were delivered to all patients. No grade III/IV toxicity was observed. In the cisplatin-capecitabine study 21 patients have completed treatment; one had to stop due to cisplatin allergy. Grade III toxicity consisted of neutropenia (n = 1); dysphagia (n = 1) and hand–foot syndrome (n = 1). One patient developed grade IV leucopenia (cisplatin 5 mg/m^2; capecitabine 575 mg/m^2 bid). In 3 additional patients in this dose level, no other DLT's have occurred. In the next dose level (cisplatin 6 mg/m^2; capecitabine 650 mg/m^2 bid) one patient developed grade IV trombopenia, so 3 extra patients will be accrued. There were no toxicity-related deaths.
Conclusions: In these two ongoing dose escalating studies with capecitabine and cisplatin given concurrently with radiation in postoperative chemoradiotherapy in gastric cancer, no non-manageable acute toxicity was observed until so far. Final results of acute toxicity are anticipated in the near future.

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Late renal toxicity following post-operative chemoradiotherapy in gastric cancer

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Background: Recent data indicate that post-operative chemoradiotherapy (CRT) improves clinical outcome in gastric cancer and that acute toxicity is acceptable. Data on late side effects, however, are scarce. Renal functional impairment represents one of the most serious late complications following abdominal radiotherapy. The aim of this study is to prospectively analyze renal function in patients receiving post-operative CRT for gastric cancer.
Patients and methods: Between December 2002 and April 2005, 77 consecutive patients with T2–3N0–3M0 adenocarcinoma of the stomach received post-operative CRT. Radiation (AP-PA technique) was given in 25 fractions of 1.8 Gy to a total dose of 45 Gy in 5 weeks. For plan comparison, dose distribution was recalculated in a subset of patients using an intensity-modulated radiotherapy (IMRT) set up. Concurrent chemotherapy consisted of 5FU (n = 12), capecitabine (n = 41) or capecitabine/cisplatin (n = 24). The relative renal function was assessed by ^{99m}Tc-MAG-3 renography before and every 6 months after treatment.
Results: The mean volume (±SD) of the left and right kidney receiving *30 Gy (V30) was 62±25%, and 14±13%, respectively. The mean dose (±SD) to the left and right kidney was 31±9 Gy and 11±6 Gy, respectively. IMRT reduced the mean dose and V30 to the left kidney with 37% and 69%, respectively, while the dose to the right kidney and liver remained within the same range. With this IMRT technique an adequate dose coverage of the target volume was ensured. At the time of analysis, 28 out of 77 patients had received a baseline and at least 1 post-treatment renography. Baseline renal tests were normal in all patients. At 12 months after CRT the relative left kidney function had decreased to a mean (±SD) of 73±23% of pretreatment value.
Conclusions: At 1 year after CRT for gastric cancer a more than 25% decrease in left renal function is observed. Given the progressive nature of radiation nephropathy, this functional impairment will continue to increase over time. Therefore, IMRT should be used to minimize the dose to the kidneys and limit late renal toxicity in these patients.

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Mature results of the French collaborative Phase II trial FFCD 9704-SFRO: preoperative concurrent chemoradiation in resectable pancreatic adenocarcinoma

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Over 80% of patients (pts) who undergo a potentially curative resection for pancreatic cancer develop local or distant recurrence. Neoadjuvant chemoradiotherapy might offer several potential advantages to these pts. In order to allow for further investigations in the neoadjuvant setting, we prospectively explored the feasibility of a chemoradiation regimen to pts with biopsy proven, potentially resectable pancreatic adenocarcinoma. The treatment scheme consisted of concomitant radiotherapy (50 Gy within 5 weeks directed at the pancreatic tumor and regional lymphatics)

with 5-fluorouracil protracted venous infusion (300 mg/m^2/day, 5 days/7, during 5 consecutive weeks) and Cisplatinum (20 mg/m^2/day, D1–5 and D 29–33), followed by a complete restaging evaluation 3–4 weeks after chemoradiation. Those without disease progression underwent immediate surgery. This study enrolled, over 4 years, 41 pts (61% men, mean age 59 years (range 33–75), with toxicity and survival data available for 40. Median tumor size was 3.1 cm, 9 pts presented positive nodes at CT scan and/or ultrasonography. All pts completed radiation, 37/41 (90%) received at least 46 Gy, 30/41 (73%) received at least 75% of the chemotherapy dose. Twenty six patients (63%) underwent a curative surgical resection, 6 had a palliative anastomosis, 4 a laparotomy, 5 (12%) did not undergo surgery due to distant disease progression at restaging. Thirty day post-operative mortality was 0.24%. Four patients presented a grade 4 (G4) hematological toxicity, 1 had a G4 postoperative sepsis, 1 died of late sepsis at 2 months post-surgery. Pathological findings show, in 11/26 pts (46%) more than 80% strongly alterated malignant cells, associated with necrotic areas in 72% of cases. One pathological complete response has been described. The feasibility of this preoperative concurrent chemoradiation regimen was established (67.5%); disease progression during the the 9–11 week preoperative period was rare (12%); 63% of all pts underwent a potentially curative resection. Toxicity was manageable and did not prevent successful surgery. This scheme compares favorably to other studies, and can now be tested on a phase III setting. Definitive data will be presented during the meeting.

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Clinical results of inoperable hepatocellular carcinoma treated with three-dimensional conformal radiotherapy: factors affecting the tumor response and survival rate

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Purpose: To evaluate the clinical results of factors affecting tumor response and survival rate of patient with hepatocellular carcinoma (HCC) treated with three-dimensional conformal radiotherapy (3D-CRT).
Materials and methods: From 1998 to 2004, 49 patients (pts) with HCC were treated with 3D-CRT. They were not indicated for surgery. Their characteristics were follows: mean age 68.5 years old (41–85 y.o.); performance status (PS): 35 pts in 1, 12 pts in 2, and 2 pts in 3; Child-Pugh classification: 23 pts in class A, 19 in B, and 7 in C; UICC (2002) stage: 23 pts in II, 27 in III, and 19 in IV. 15 pts had ascites before 3D-CRT. 32 pts were treated for main hepatic tumor, 15 for PV tumor thrombi, and 2 for IVC thrombi. The mean tumor size was 4.3 cm (range 1.3–12 cm). The mean radiation dose was 44 Gy (15–60 Gy) in a daily fraction of 2–3 Gy using 10-MV linear accelerator. The mean biologic effective dose at $\alpha/\beta = 10$ was 44.7 Gy. Tumor response was evaluated by the change in maximum diameter detected on CT and MRI images 1–3 months after radiotherapy. The variability of age, PS, Child-Pugh classification, UICC stage, ascites, PV/IVC tumor thrombi, tumor size and radiation dose was evaluated between complete response (CR) + partial response (PR) group and no change (NC) + progressive disease (PD) group. The factors associated with survival were also evaluated by using Cox regression model. Lesion-to-liver contrast-to-noise ratio (CNR), signal-to-noise ratio (SNR), and standard deviation (SD) were evaluated on T2 weighted MR imaging before and after radiotherapy in 38 patients.
Results: The mean follow-up was 9 months (2–40 months). 16 patients (33%) got PR, 22 (45%) NC, 11 (22%) PD, and no patient got CR. The tumor response rate (CR+PR) was 33%. Radiation dose was the only significant factor for tumor response on Mann-Whitney U-test ($p < 0.05$). The over all survival rate at 1 and 2 year was 49.6% and 24.3%, respectively (median survival 14.5 months). On univariate analysis, PS, Child-Pugh classification, PV tumor thrombi and ascites were significant factors for survival rate ($p < 0.05$). On multivariate analysis, PS was only significant factor. In PR group, CNR after radiotherapy was significantly higher than before ($p < 0.01$).
Conclusions: Radiation dose was significant factor in tumor response, while tumor size and PV/IVC tumor thrombi were not significant. CNR was useful to evaluated tumor response of the patient with HCC treated with 3D-CRT. Additional efforts for dose escalation may be warranted to improve the treatment results.

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Histological results of endoscopic resection for esophageal lesions diagnosed as high-grade intraepithelial squamous neoplasia by endoscopic biopsy

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Background: The ability to detect early squamous neoplasia of the esophagus can be enhanced considerably by iodine staining during endoscopic examination. Histologically, biopsy specimens obtained from the lesion detected in endoscopic screening were often diagnosed as high-grade intraepithelial squamous neoplasia (WHO 2000). However, there are very few reports on the characteristics of such intraepithelial squamous lesions, and a management strategy for such lesions has therefore not been established. In this study, we prospectively performed endoscopic mucosal resection (EMR) for esophageal lesions diagnosed as high-grade intraepithelial squamous neoplasia by endoscopic biopsy and investigated histological features of the lesions in totally resected specimens.
Patients and methods: During the period from April 2001 to September 2004, 51patients were found to have lesions diagnosed as high-grade intraepithelial squamous neoplasia of the esophagus by endoscopic biopsy at Hokkaido University Hospital and associated hospitals. All patients underwent EUS with the use of a high-frequency catheter probe and were confirmed to have no evidence of submucosal tumor invasion. Subsequently, all patients underwent EMR at Hokkaido University Hospital.
Results: Histological examination of totally resected specimens revealed that 12 (23.5%) of the 51 patients had tumor invasion of the basement membrane that was confined to the lamina propria mucosae and that 4 (7.8%) of the 51 patients had tumor invasion of the muscularis mucosae. The remaining 35 patients (68.6%) were confirmed to have high-grade intraepithelial squamous neoplasia of the esophagus. The invasive focus all of the 16 lesions of invasive squamous cell carcinoma was surrounded by high-grade intraepithelial squamous neoplasia.
Conclusions: Histological results suggested that high-grade intraepithelial squamous neoplasia of the esophagus has characteristics of carcinoma in the pre-invasive stage. EMR, which can be employed both therapeutically and diagnostically, should be performed for esophageal lesions diagnosed by endoscopic biopsy as high-grade intraepithelial squamous neoplasia not only because of its probable malignant potential but also because over 30% of such lesions are actually invasive carcinoma.

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Postoperative adjuvant gemcitabine alone and concurrent with radiation after resection of locally advanced pancreatic carcinoma

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Purpose: Gemcitabine is a pyrimidine analogue which has potential activity in advanced pancreatic cancer and is a powerful radiosensitizer. We evaluated the efficacy and toxicity of postoperative administration of Gemcitabine (GEM) alone, followed by concurrent GEM and irradiation (RT) after resection for locally advanced pancreatic adenocarcinoma.
Methods and materials: Between 1999–2004, thirty-three patients (median age 58 years, range 21–78, median Karnofsky Performance Status 90, range 70–100) with stage II (7 patients) and stage III (26 patients) resected pancreatic adenocarcinoma were treated. Twenty-nine patients (88%) had RO and four patients (12%) had R1 resection. GEM 1000 mg/m^2 on D1, 8, 15 was given within a median of 32 (range 21–103 days) days after surgery, followed by GEM 300 mg/m^2 weekly concurrent with radiotherapy (50.4 Gy in 180 cGy daily fractions(. After the completion of chemoradiotherapy, patients received three additional courses of GEM 1000 mg/m^2 on D1, 8, 15 in one cycle. Each cycle consisted of 3 weeks of treatment followed by a 2 week chemotherapy free interval.
Results: Twenty-four (73%) patients received 4 to 6 courses of weekly GEM, eight patients received 2 to 3 courses and one patient could not receive any. Grade III-IV hematologic toxicity, mainly leuocopenia occurred only in 3 (9%) patients. Grade I and II gastrointestinal toxicity (nausea, vomiting) occurred in 9 patients (27%), whereas grade III or IV gastrointestinal toxicity was not observed. Concurrent gemcitabine and radiotherapy was completed without treatment interruptions in 33% of the patients. Median treatment interruption was 3 days (range 1–26 days). Twenty-seven patients (81.8%) received GEM after chemoirradiation. During a median follow-up of 35 months (range, 12–68) local recurrence was observed in 4 (three of them had peritoneal seeding or distant