Conclusion: The proposed aggressive treatment program of gastric cancer is feasible, well tolerated and is able to induce a high loco-regional tumor control rate

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#### Clinical study on intraperitoneal hyperthermic perfusion chemotherapy for patients with gastric cancer

X.F. Cao<sup>1</sup>, W.M. Wu<sup>2</sup>, H.Y. Qiu<sup>1</sup>, B.C. Wu<sup>1</sup>, M.H. Cai<sup>1</sup>, W.Z. Za<sup>3</sup>. <sup>1</sup> Yan Cheng Cancer Hospital, Jiang Su Province; <sup>2</sup>The Affiliated Hospital of Nei Meng Gu Medical College, <sup>3</sup>The first People's Hospital of Yan Cheng, Jiang Su Province, China

**Purpose:** The prognosis of patients with gastric cancer treated by only surgery are mostly still bad in China. We used intraperitoneal hyperthermic perfusion chemotherapy to hope to increase resection rate and survival rate, and to prevent the side effects of systemic chemotherapy.

Methods: 420 cases with gastric cancer were divided into five groups. Both Group A and Group B have 60 cases. Whereas Group A received neo-adjuvant intraperitoneal hyperthermic perfusion chemotherapy, Group B did not. Group C, Group D and Group E have 100 cases for each group. Group C received intraperitoneal hyperthermic perfusion chemotherapy; Group D accepted adjuvant chemotherapy; Group E did not received chemotherapy.

**Results:** The resection rate for Group A was 98.33% (59/60), whereas the resection rate for Group B was 86.33% (53/60) (p < 0.05). The rate of side effects of chemotherapy for Group C was 8% (II°), 2% (III°), 1% (IV°), which were lower than 30% (II°), 12% (III°), 6% (IV°) for group D respectively (p < 0.05). The 1 year and 3 year survival rates for Group A and Group C were higher than respective ones for Group B and Group C/D (p < 0.05).

Conclusion: Intraperitoneal hyperthermic perfusion chemotherapy may increase the resection rate and survival rate and prevent the side effects of chemotherapy. The exact value of intraperitoneal hyperthermic perfusion chemotherapy are worth further randomized study.

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#### Evaluation for multiple cancer in cases of endoscopic mucosal resection for early gastric carcinoma

T. Suzuki, T. Nakamura, A. Matsu-ura, K. Yamao, K. Ohashi. Dept. of Gastroenterology, Aichi Cancer Center Hospital, Nagoya, Japan

Purpose: Endoscopic mucoal resection (EMR) for early gastric carcinoma is a safe and minimally invasive treatment. Meanwhile, there is a need for the continued endoscopic surveillance in search of metachronous multiple lesion. This is because the patient treated with EMR has a whole stomach, the mucosa of which is considered to have a potential for carcinogenesis. In this study, we investigated the clinicopathological features of multiple gastric cancers in the patients who were treated by EMR.

Methods: The indications for EMR were those approved by the Japanese Endoscopy Society. The resection method used was double-channel technique with saline injection into the submucosa. A total of 115 patients (84 men, 31 women, mean age 66.6 years) with 127 lesions underwent EMR during the last 7 years. They were endoscopically followed every 3 months in the first year, and annually thereafter.

Results: Multiple gastric cancer was observed in 14 patients (12.2%) with 31 lesions. Double cancer was found in 11 patients, of which 5 were synchronous and 6 were metachronous. Gross appearances of the lesions were elevated-type (E)-E in 5, depressed-type (D)-D in 5, and E-D in one. In 7 of 11 cases, lesions occupied the same one-third of the stomach: middle one-third in 4 and lower one-third in 3. Triple cancer was found in 3 patients. Of these, all lesions were metachronous in 2 cases, whereas 2 lesions were synchronous in the remaining case. For these patients, gross appearance was D-D-D in 2 and E-D-D in one.

Conclusions: The incidence of multiple cancer in the EMR cases was proved to be high. The multiple lesions were liable to appear in the same macroscopic form and location. It is advisable to be aware of the possibility of finding the multiple lesions both before and after the EMR.

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## Expression of thymidylate synthase and its prognostic value in gastric carcinoma with adjuvant 5-fluorouracil containing chemotherapy

H.Y. Lim<sup>1</sup>, J.H. Choi<sup>1</sup>, H.S. Kim<sup>1</sup>, D.K. Nam<sup>1</sup>, H.C. Kim<sup>1</sup>, H.J. Joo<sup>2</sup>. <sup>1</sup>Ajou University School of Medicine, Hematology & Oncology, Suwon; <sup>2</sup>Ajou University School of Medicine, Pathology, Suwon, South Korea

**Purpose:** The antimetabolite 5-fluorouracil (5-FU) is one of the most common chemotherapeutic agents for gastric carcinoma. Thymidylate synthase (TS) is the target enzyme for 5-FU and intratumoral expression of TS may predict an inverse relationship to response and survival for patients who receive 5-FU containing chemotherapy. We investigate the expression of TS and its prognostic value in gastric cancer patients with adjuvant 5-FU containing chemotherapy after curative resection.

**Methods:** We obtained tissue specimens from 104 patients of surgically resected stage II and III gastric adenocarcinoma. All patients received adjuvant chemotherapy containing 5-FU after curative resection and extensive lymph node dissection. We performed immunohistochemical studying for TS with anti-TS antibody in gastric carcinoma.

**Results:** The positive rate of TS expression was 76.9% in 104 gastric cancers. The group with high and low TS expression consisted of 51.0% and 49.0%, respectively. The differences in recurrence and death rate between TS positive group and negative group were not significant (DFS 61.3% vs. 58.3% p = 0.732, OS 63.8% vs. 58.3% p = 0.625, respectively).

**Conclusion:** Our results suggest that TS expression alone could not predict the recurrence and survival in gastric carcinoma with adjuvant 5-FU containing chemotherapy after curative resection.

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### Effects of high dose-rate intraluminal brachytherapy (HDR-ILBRT) for the patients with esophageal squamous cell carcinoma (SCC)

M. Iwasa<sup>1</sup>, Y. Iwasa<sup>1</sup>, Y. Ohmori<sup>1</sup>, M. Kume<sup>1</sup>, S. Ogoshi<sup>1</sup>, Y. Ogawa<sup>2</sup>, S. Yoshida<sup>2</sup>. <sup>1</sup>Department of Surgery II; <sup>2</sup>Radiology Kochi Medical School, Nankoku, Kochi, Japan

**Background:** The effectiveness of the multimodal treatment for the patients with esophageal SCC with HDR-ILBRT by 60 Co as a component of treatment was evaluated clinically.

Patients and Treatment Methods: 167 patients with esophageal cancer were divided into 4 treatment groups with or without operation and HDR-ILBRT: Group A: 71 patients were performed radical operation, external irradiation and HDR-ILBRT; Group B: 30 patients underwent operation and external irradiation only; Group C: 28 patients with external irradiation and HDR-ILBRT; Group D: 38 patients with external irradiation alone and no other modality.

**Results:** 5-year survival rate of Group A and B was 63% and 20%, respectively (p < 0.001). Mean Survival time and 5-year survival rate of Group C (15.3  $\pm$  1.5 months and 20%) were significantly improved compared to Group D (p < 0.001). There was no 5-year survival in the patients without brachytherapy.

**Conclusion:** These results strongly suggest the use of HDR-ILBRT as a component of multimodal treatment in patients with esophageal cancer is a reasonable approach and HDR-ILBRT significantly improves the effects of external beam irradiation therapy.

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#### Effect of T and N stages on outcome of chemoradiation for carcinoma of anus

S. Ngan<sup>1</sup>, J. Smith<sup>2</sup>, M. Chao<sup>1</sup>, D. Lim-Joon<sup>1</sup>. <sup>1</sup>Peter MacCallum Cancer Institute, Radiation Oncology, Melbourne; <sup>2</sup>Peter MacCallum Cancer Institute, Statistic Centre, Melbourne, Australia

**Purpose:** Chemoradiation has become the standard of care in management of anal cancer. Pathologic confirmation of the clinical stage is usually not available. This study was designed to investigate the effect of T and N stages in patients with carcinoma of anus treated with modern combined radiotherapy and chemotherapy.

Methods: Patients with localized squamous carcinoma of anus treated with curative intent with chemoradiation between 1 January 1982 and 31 December 1996 were identified from the anal cancer database at Peter MacCallum Cancer Institute. The standard protocol during this period consisted of radiotherapy of 54 Gy in 30 fractions with chemotherapy 5-FU

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1 gm/m $^2$  on days 1–4 and days 29–32 and a bolus dose of mitomycin C 10 mg/m $^2$  on day 1

Results: A total of 96 patients satisfied the inclusion criteria, 70% female. The median age was 62 years (range 33–86). T stages at presentation were: Tx 2%, T1 18%, T2 50%, T3 9%, T4 21%. Thirteen patients (14%) had involved inguinal nodes. Disease persisted after chemoradiation in 10%. At 10 years following commencement of radiotherapy a further 19% were estimated to have suffered locoregional relapse, 6% distant metastases and 19% death without known progression, leaving 46% surviving failure-free at 10 years. Estimated overall survival was 91% at 2 years, 72% at 5 years and 59% at 10 years. There were no significant differences in failure-free survival between T stages-T1, T2, T3, T4, between N0 and N1–3, between T1–2N0 and T3/T4/N1–3. Patients with tumours <4 cm survived significantly longer without failure than patients with larger tumours (P = 0.006). In terms of overall survival, there were no significant differences between T stages, between N0 and N1–3, between T1-2N0 and T3/T4/N1–3, or between <4 cm and >4 cm tumours.

Conclusion: In our experience, TNM stage for carcinoma of anus does not predict failure-free survival or overall survival in patients treated with chemoradiation.

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# A phase II study of hypofractionated radiotherapy in combination with Gemcitabin in the palliative treatment of advanced pancreatic carcinoma

I.E. Antonisse<sup>1</sup>, C.J. van Groeningen<sup>2</sup>, J.A. Langendijk<sup>1</sup>, B.J. Slotman<sup>1</sup>.

<sup>1</sup>University Hospital Vrije Universiteit, Radiation Oncology, Amsterdam;

<sup>2</sup>University Hospital Vrije Universiteit, Medical Oncolog, Amsterdam, Netherlands

**Purpose:** To evaluate the toxicity and palliation of hypofractionated radiotherapy in combination with gemcitabine in advanced inoperable pacreatic carcinoma.

Patients and Methods: A total number of 21 patients with recurrent disease after resection, primary irresectable and/or metastatic tumours were included. Gemcitabine (300 mg/m²) was given at day 1, 8 and 15 at the same day of radiotherapy. CT-assisted radiotherapy consisted of 3 fractions of 8 Gy, once a week on the macroscopic tumour. From day 22, gemcitabine (1000 mg/m²) was continued weekly. The mean number of courses was 12 (3–21). At most all patients suffered from intractable abdominal pain.

Results: Treatment was generally well tolerated. Seventeen patients experienced mild nausea and vomiting and 7 patients experienced mild abdominal pain. In 7 patients, an increase of pre-existing pain was noted shortly after radiation. In 1 patient gemcitabine was not given before the third fraction because of hematological toxicity and in 6 patients dose reduction was needed. No significant changes of liver enzymes and renal function were noted. A significant reduction of the turnour marker CA 19.9 was observed in 14/17 patients (82%). Palliation of pain was observed in 13/18 patients (72%). Pain medication could be reduced in 11/15 patients (73%). The median survival was 16.2 months.

**Conclusion:** Hypofractionated radiotherapy in combination with gemcitabine in irresectable pancreatic carcinoma is well tolerated and offers good palliation.

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### Phase I/II study of irinotecan combined with mitomycin-C in patients with advanced gastric cancer

T. Yamao<sup>1</sup>, M. Maruyama<sup>1</sup>, K. Shirao<sup>2</sup>, Y. Matsumura<sup>2</sup>, Y. Yamada<sup>2</sup>, K. Muro<sup>2</sup>, K. Sugano<sup>2</sup>, Y. Shimada<sup>2</sup>. <sup>1</sup> Cancer institute hospital, department of medicine, Tokyo; <sup>2</sup> National cancer center hospital, department of medicine, Tokyo, Japan

Purpose: Irinotecan (CPT-11) is a new active drug for advanced gastric cancer (AGC). Preclinical synergism has been reported in combination of CPT-11 and mitomycin-C (MMC) in human gastric cancer cell lines. To determine the maximum tolerated dose (MTD), the dose limiting toxicity (DLT), and preliminary anti-tumor activity, we conducted a dose escalation study of CPT-11 and MMC in patients with AGC.

**Methods:** MMC was administered as i.v. bolus, and then immediately followed by intravenous infusion of CPT-11 over 90 minutes. The treatment was repeated every other week. Granisetron was administered to prevent nausea and vomiting. The prophylactic use of granulocyte colony-stimulating factor was not planned. The planned dose escalation schedule for MMC/CPT-11 (mg/m²) of each dose level was as follows; level-1, 5/100;

level-2, 5/125; level-3, 5/150; level-4, 7/150; level-5, 10/150. MTD is determined when the incidence of critical toxicity (either grade 4 neutropenia "4 days, febrile grade 4 neutropenia, non-hematological toxicity "grade 3, or treatment delay due to any toxicity >7 days) exceeds 50% (2/3 or 3/6 patients).

Results:: Twenty-one patients was entered (3 at level-1, 7 at level-2, 6 at level-3, 3 at level-4, and 2 at level-5, respectively) and 20 patients were evaluable for toxicity. Patient characteristics were following; median age 61 yrs [range 46-73]; sex 18 male, 3 female; PS 0-4, 1-15, 2-2; macroscopic type; diffuse -4, non-diffuse -17; microscopic type; diffuse 19, intestinal -2. At level-1, no critical toxicity was observed. At level-2, the critical toxicity was observed in 2 of 7 patients (administration delay due to persistent leukopenia and grade 4 diarrhea). At level-3, the critical toxicity was observed in 2 of 6 patients (grade 4 neutropenia "4 days and grade 3 diarrhea). At level-4, no critical toxicity was observed. At level-5, the critical toxicity was observed in 2 patients (administration delay due to hematological toxicity and grade 3 diarrhea). At the present, partial responses were achieved in 8 of 16 patients evaluated (response rate; 50%). In eight chemotherapy-naive patients, partial responses were obtained in 6 patients (response rate; 75%). The chemotherapy could be continued on the outpatient-basis in all patients.

Conclusions: We determined that the maximum tolerated dose of CPT-11 and MMC was 150 mg/m² and 10 mg/m², respectively and that the recommended dose of CPT-11 and MMC for a phase II trial was 150 mg/m² and 7 mg/m², respectively. Additionally, the present study suggested the combination chemotherapy with CPT-11 and MMC should be very active against advanced gastric cancer. We will soon start a phase II study of this regimen.

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#### Stage-adapted radio-chemotherapy in anal canal carcinoma

C. Landmann, B. Amsler. Radiation-oncology, University Hospital Basel, Basel, Switzerland

**Purpose:** The optimal combination of radio-chemotherapy in anal canal carcinoma has yet to be established. The advantages of stage-adapted therapy and the merits of different radio-chemotherapy combinations in advanced stages are analyzed.

Methods: 56 patients with anal canal carcinoma with a median age of 64 years (range 29–92) were treated. Median follow-up was 28 months (range 10–75 months). 8 patients with early stages received only local irradiation up to 60 Gy, 19 patients with T2 N0 stages were treated with a combination of 5-FU and 50 Gy, 29 patients with advanced stages received 50 Gy combined with 5-FU and Mitomycin C (14 patients) or 5-FU and Cisplatin (15 patients).

**Results:** Overall-survival was 80%, disease-survival 60% at 5 years. The local recurrence rate was 22%. None of the patients treated with a combination containing Cisplatin developed distant metastasis as compared to 36% in the Mitomycin C group.

**Conclusion:** Early stage patients can be successfully treated with irradiation alone or combined only with 5-FU. Advanced cases seem to profit more from a combined radio-chemotherapy regimen containing Cisplatin.

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#### Hepatocellular carcinoma: Adjuvant chemotherapy postliver transplant

M.J. Villanueva, F. Navarro, A. Sanchez, M. Provencio, F. Bonilla, V. Cuervas-Mons, P. España. Service of Medical Oncology, Clínica Puerta de Hierro, Universidad Autónoma de Madrid, Spain

Background: Transplantation is sometimes recommended for hepatocellular carcinoma (HCC). Patients with cirrhosis in stage II to IVA have a median survival of 12 months following surgical resection or other local therapies. More than 86% of patients have a recurrence within the following 2 years. Liver transplantation has been occasionally used in these patients, with or without complementary chemotherapy.

Materials and Methods: Between 1992 and 1998, 9 patients underwent transplantation and subsequently received weekly doses of adjuvant doxorubicin 10 mg/m², for 20 weeks. All patients had hepatocarcinoma. Eight patients had cirrhosis (44.4% C virus, 0% B virus, 22.2% alcoholic, 22.2% cryptogenic, 0% metabolic hepatopathy). One patient had chronic active hepatitis. Classification was 33.3% stage II, 22.2% stage III, and 44.4% stage IV-A. Major vascular invasion was seen in 11.1%, microscopic invasion in 22.2%, and 44.4% had capsular invasion (11.1% pT2). Single tumorous nodules were found in 33.3%, multiple tumorous nodules in 1