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## **Trends for the Past 10 Years and International Comparisons of the Structure of Korean Radiation Oncology**

### Objective

Study aims include determination of nationwide structural characteristics of radiation oncology facilities, types of radiation therapy equipment, availability of human resources and trends and comparisons with previous surveys.

### Methods

An annual nationwide survey was conducted to collect the statistics of infrastructure since 1997. All requested questionnaires have been identical for 10 years. The questionnaires included status on basic radiation therapy facilities, human resources and radiation therapy equipment. Journal and statistical data reviews were performed to evaluate the structure of other countries.

### Results

Radiation oncology facilities have steadily increased for 10 years and reached 60 sites in 2006. Also a steady increase of 1.5 times for linear accelerators, 5.8 times for computed tomography simulators and 3.0 times for radiation treatment planning systems was noted. Meanwhile, cobalt-60 teletherapy units and hyperthermia equipment had steadily decreased for 10 years. The number of human resources has steadily increased for the past 10 years, especially for radiation therapy technologists. However, radiation therapy equipment and human resources per population are relatively low compared with advanced countries.

### Conclusions

This study will assist preparation of the administrative planning policy of radiation oncology and should be useful to indicate the direction of future development and educational training programs in Korea and possibly in other countries.

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## **Usefulness of Narrow-band Imaging for Detecting the Primary Tumor Site in Patients with Primary Unknown Cervical Lymph Node Metastasis**

## Objective

We sometimes experienced patients with primary unknown cervical lymph node metastasis. In such cases, if computed tomography, magnetic resonance imaging, laryngoscopy and gastrointestinal endoscopy cannot detect a primary site, there is no other effective method to identify a possible primary tumor. We investigated whether narrow-band imaging can detect a possible primary tumor in such.

## Methods

Forty-six patients with primary unknown cervical lymph node metastasis were surveyed about primary tumors, from January 2003 to December 2006. All cervical lymph nodes were histologically proved to be squamous cell carcinoma by fine-needle aspiration cytology. Narrow-band imaging combined with magnifying endoscopy was used to identify the primary site in the head and neck region and cervical esophagus. Histological analysis was performed for all suspicious lesions by a biopsy specimen.

## Results

Twenty-six lesions were suspected to be cancerous lesions by narrow-band imaging in the head and neck region. Sixteen lesions in 16 (35%, 16/46) patients were squamous cell carcinoma. Ten lesions were located in the hypopharynx and the remaining six lesions were located in the oropharynx. White light endoscopy could not point out any lesion.

## Conclusions

Narrow-band imaging endoscopy can detect possible primary cancer in patients with primary unknown cervical lymph node metastasis.

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## **Human Papillomavirus DNA in Plasma of Patients with HPV16 DNA-positive Uterine Cervical Cancer**

### Objectives

The squamous cell carcinoma antigen is considered the most accurate serologic tumor marker for uterine cervical carcinoma. However, serum squamous cell carcinoma antigen levels were found to correlate significantly with clinical severity of atopic dermatitis and chronic renal failure. The present study was conducted in patients with human papillomavirus 16 DNA-positive uterine cervical cancer to determine the plasma level of human papillomavirus 16 DNA and the diagnostic values of plasma human papillomavirus DNA in these patients.

### Methods

Forty-three human papillomavirus 16-positive patients with cervical intraepithelial neoplasia or uterine cervical squamous cell carcinoma were recruited in this study. The diagnosis was cervical cancer in 20 patients, high-grade squamous intraepithelial lesions in 21, low-grade squamous intraepithelial lesions in 1 and negative for intraepithelial lesion or malignancy in 3 patients. Before any treatment, blood samples were collected from all patients. For analysis of human papillomavirus DNA in plasma of patients with cervical cancer, quantitative polymerase chain reaction fluorescent assay for human papillomavirus 16 was performed using human papillomavirus 16 primers and SYBR Green dye using the LightCycler 480 SW1.5 apparatus.

### Results

Plasma human papillomavirus 16 DNA was detected in only 30.0% of the patients with human papillomavirus 16-positive cervical cancer and in none of normal controls. The copy number of plasma human papillomavirus 16 DNA was higher in patients with invasive cancer than in those with cervical intraepithelial neoplasia (CIN3), micro-invasive cancer and in normal individuals.

### Conclusions

These results indicated that the plasma human papillomavirus DNA level could be potentially used as a marker of low-invasive cervical cancer tumors in patients with normal squamous cell carcinoma antigen levels before treatment.

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## **Phase I and Pharmacokinetic Study of ABI-007, Albumin-bound Paclitaxel, Administered Every 3 Weeks in Japanese Patients with Solid Tumors**

### **Objective**

ABI-007 is a novel Cremophor® EL-free nanoparticle albumin-bound paclitaxel. This Phase I study was designed to evaluate tolerability and determine recommended dose for Japanese patients when ABI-007 was administered in every-3-week schedule. Pharmacokinetics of paclitaxel was also assessed.

### **Methods**

Patients with advanced solid tumors refractory to standard therapy received a 30 min intravenous infusion of ABI-007 every 3 weeks without pre-medications at 200, 260 or 300 mg/m<sup>2</sup>, respectively. Tolerability and recommended dose were determined by the standard '3 + 3' rule.

### **Results**

No dose-limiting toxicity was observed, despite the dose escalation. In another cohort, 260 mg/m<sup>2</sup> was re-evaluated and resulted in no dose-limiting toxicity. Grade 3 or 4 neutropenia was reported for the majority of patients (n = 8) but no incidence of febrile neutropenia. Non-hematological toxicities were generally mild except for Grade 3 sensory neuropathy (n = 3). Pharmacokinetic study demonstrated the area under the curve of paclitaxel increased with increasing the dosage, and comparable pharmacokinetic parameters to the western population. Partial response was observed in three non-small cell lung cancer patients. Two of whom had received docetaxel-containing chemotherapy prior to the study.

### **Conclusions**

ABI-007 administered in every-3-week schedule was well tolerated up to 300 mg/m<sup>2</sup>, and recommended dose was determined at 260 mg/m<sup>2</sup> in consideration of efficacy, toxicities and similarity of pharmacokinetic profile in western studies. Additional studies of single-agent ABI-007 as well as platinum-based combinations, particularly in patients with non-small cell lung cancer, are warranted.

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## **A Consensus-based Guideline Defining the Clinical Target Volume for Pelvic Lymph Nodes in External Beam Radiotherapy for Uterine Cervical Cancer**

## Objective

To develop a consensus-based guideline as well as an atlas defining pelvic nodal clinical target volumes in external beam radiotherapy for uterine cervical cancer.

## Methods

A working subgroup to establish the consensus-based guideline on clinical target volumes for uterine cervical cancer was formulated by the Radiation Therapy Study Group of the Japan Clinical Oncology Group in July 2008. The working subgroup consisted of seven radiation oncologists. The process resulting in the consensus included a comparison of contouring on CT images among the members, reviewing of published textbooks and the relevant literature and a distribution analysis of metastatic nodes on computed tomography/magnetic resonance imaging of actual patients.

## Results

The working subgroup defined the pelvic nodal clinical target volumes for cervical cancer and developed an associated atlas. As a basic criterion, the lymph node clinical target volume was defined as the area encompassed by a 7 mm margin around the applicable pelvic vessels. Modifications were made in each nodal area to cover adjacent adipose tissues at risk of microscopic nodal metastases. Although the bones and muscles were excluded, the bowel was not routinely excluded in the definition. Each of the following pelvic node regions was defined: common iliac, external iliac, internal iliac, obturator and presacral. Anatomical structures bordering each lymph node region were defined for six directions; anterior, posterior, lateral, medial, cranial and caudal. Drafts of the definition and the atlas were reviewed by members of the JCOG Gynecologic Cancer Study Group (GCSG).

## Conclusions

We developed a consensus-based guideline defining the pelvic node clinical target volumes that included an atlas. The guideline will be continuously updated to reflect the ongoing changes in the field.

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## **Combination Therapy of Interleukin-2 and Sorafenib Improves Survival Benefits and Prevents Spontaneous Pulmonary Metastasis in Murine Renal Cell Carcinoma Models**

### Objective

The objective of this study was to evaluate the benefits of combination therapy consisting of recombinant human interleukin-2 and sorafenib for survival efficacy and the suppression of metastasis in murine renal cell carcinoma models.

### Methods

Lung-metastasized renal cell carcinoma mice were treated with various combinations of recombinant human interleukin-2 and sorafenib. Tumor growth was observed using a bioluminescence imaging system. Next, the nephrectomized renal cell carcinoma mice were administered various combinations of recombinant human interleukin-2 and sorafenib, followed by a lung resection in order to examine lung metastasis by bioluminescence imaging.

### Results

The increased life-span ratio in mice receiving combination therapy was 1.45, whereas that in mice treated with sorafenib or recombinant human interleukin-2 alone therapy was 1.28 and 1.07, respectively. The concomitant administration of recombinant human interleukin-2 and sorafenib had a metastasis-inhibitory effect, whereas the other treatments failed.

### Conclusions

These findings indicate that combination therapy of recombinant human interleukin-2 and sorafenib may offer better outcomes than either monotherapy with recombinant human interleukin-2 or sorafenib with respect to survival benefits and the prevention of pulmonary metastasis in renal cell carcinoma patients.

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## Clinical Utility of the 70-gene MammaPrint Profile in a Japanese Population

### Objective

van't Veer and colleagues developed a 70-gene prognosis profile known as MammaPrint to identify breast cancer patients who were at low risk of developing metastases. We evaluated the prognostic value of the 70-gene MammaPrint profile in Japanese women with node-negative breast cancer.

### Methods

Frozen tumour samples from 102 eligible node-negative breast cancer patients aged 70 or younger were characterized with the MammaPrint array. The patients were treated with breast-conserving therapy or mastectomy with axillary lymph node dissection between December 1998 and August 2001. About 73 percent received adjuvant hormonal therapy and 28 percent received adjuvant chemotherapy. The gene expression profiles obtained by MammaPrint classified the patients as high- or low-genomic risk. The median follow-up was 7.1 years.

### Results

Among the 102 patients, 20 (20%) were classified as low-genomic risk and 82 (80%) were classified as high-genomic risk. The probability of distant metastasis-free survival at five years was 100% for the low-risk group and 94% for the high-risk group.

### Conclusions

The 70-gene MammaPrint prognosis profile accurately identified Japanese breast cancer patients at low risk of developing recurrences. In fact, 100% of the individuals in the low-risk category remained metastasis-free for the duration of the observation period.

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## A Computer-assisted Model for Predicting Probability of Dying Within 7 Days of Hospice Admission in Patients with Terminal Cancer

### Objective

The aim of the present study is to compare the accuracy in using laboratory data or clinical factors, or both, in predicting probability of dying within 7 days of hospice admission in terminal cancer patients.

### Methods

We conducted a prospective cohort study of 727 patients with terminal cancer. Three models for predicting the probability of dying within 7 days of hospice admission were developed: (i) demographic data and laboratory data (Model 1); (ii) demographic data and clinical symptoms (Model 2); and (iii) combination of demographic data, laboratory data and clinical symptoms (Model 3). We compared the models by using the area under the receiver operator curve using stepwise multiple logistic regression.

### Results

We estimated the probability dying within 7 days of hospice admission using the logistic function,  $P = \frac{\text{Exp}(\beta x)}{1 + \text{Exp}(\beta x)}$ . The highest prediction accuracy was observed in Model 3 (82.3%), followed by Model 2 (77.8%) and Model 1 (75.5%). The  $\log[\text{probability of dying within 7 days}/(1 - \text{probability of dying within 7 days})] = -6.52 + 0.77 x (\text{male} = 1, \text{female} = 0) + 0.59 x (\text{cancer, liver} = 1, \text{others} = 0) + 0.82 x (\text{ECOG score}) + 0.59 x (\text{jaundice, yes} = 1, \text{no} = 0) + 0.54 x (\text{Grade 3 edema} = 1, \text{others} = 0) + 0.95 x (\text{fever, yes} = 1, \text{no} = 0) + 0.07 x (\text{respiratory rate, as per minute}) + 0.01 x (\text{heart rate, as per minute}) - 0.92 x (\text{intervention tube} = 1, \text{no} = 0) - 0.37 x (\text{mean muscle power})$ .

### Conclusions

We proposed a computer-assisted estimated probability formula for predicting dying within 7 days of hospice admission in terminal cancer patients.

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## Five Serum Proteins Identified Using SELDI-TOF-MS as Potential Biomarkers of Gastric Cancer

### Objective

The aims of this study were to detect serum proteomic patterns in gastric cancer serum samples using Surface-enhanced Laser Desorption/ionization-Time-of-flight-Mass Spectrometry ProteinChip array technology, to screen biomarker candidates, to build diagnostic models and to evaluate their clinical significance.

### Methods

Serum samples from patients with gastric cancer and normal healthy control subjects (n = 125) were analysed using surface-enhanced laser desorption/ionization technology. The spectra were generated on weak cation exchange (WCX2) chips, and protein peak clustering and classification analyses were established using Ciphergen Biomarker Wizard and Biomarker Pattern software, respectively. The diagnostic models were developed and validated by discriminant analysis. In addition, the results of the surface-enhanced laser desorption/ionization model were compared with the biomarkers carcinoembryonic antigen and carbohydrate antigen 199 in a subset of samples using a microparticle enzyme immunoassay.

### Results

Five protein peaks at 2046, 3179, 1817, 1725 and 1929 m/z were automatically chosen as components of the best biomarker pattern for diagnosis of gastric cancer. In addition, we identified a single protein peak at 4665 m/z, which could distinguish between stage I/II and stage III/IV gastric cancer with a specificity and sensitivity of 91.6% (11/12) and 95.4% (21/22), respectively. When this biomarker was validated in the second set of samples, the specificity and sensitivity were 91.7% (11/12) and 86.3% (19/22), respectively.

### Conclusions

The present results suggest that serum surface-enhanced laser desorption/ionization protein profiling can distinguish patients with gastric cancer, and in particular stage I/II patients, from normal subjects with a relatively high sensitivity and specificity. Surface-enhanced Laser Desorption/ionization-Time-of-flight-Mass Spectrometry is a potential new diagnostic tool for the screening of gastric cancer.

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## Predictive and Prognostic Values of Tau and ERCC1 in Advanced Breast Cancer Patients Treated with Paclitaxel and Cisplatin

### Objective

We studied tau and excision repair cross-complementing 1 expression to evaluate their predictive values in advanced breast carcinoma patients.

### Methods

Patients treated with paclitaxel and cisplatin as the first-line chemotherapy for locally advanced or metastatic breast cancer were enrolled. The expression levels of tau and excision repair cross-complementing 1 were assessed by immunohistochemistry and examined for their associations with treatment response and survival.

### Results

Fifty-four patients were included in this study. Despite the strong association between tau expression and lower histological grade and estrogen receptor expression, tau expression remained an independent predictor for a lower response rate in multivariate analysis (odd ratio = 0.24, P = 0.02). However, tau expression was a predictor for longer overall survival in both univariate analysis (median, 57.5 vs. 30.4 months, P = 0.02) and multivariate analysis (hazard ratio = 0.36, P = 0.008). Excision repair cross-complementing 1 was not associated with treatment response or overall survival.

### Conclusions

Tau expression but not excision repair cross-complementing 1 in advanced breast cancer predicts poor response to combination chemotherapy of paclitaxel and cisplatin. However, tau expression is significantly associated with longer overall survival.

## **Induction Chemotherapy with Nedaplatin with 5-FU Followed by Intensity-modulated Radiotherapy Concurrent with Chemotherapy for Locoregionally Advanced Nasopharyngeal Carcinoma**

### **Objective**

This Phase II study was conducted to evaluate the activity and feasibility of a regimen of nedaplatin and 5-fluorouracil as induction chemotherapy, followed by intensity-modulated radiotherapy concurrent with chemotherapy in patients with locoregionally advanced nasopharyngeal carcinoma.

### **Methods**

Patients received neoadjuvant chemotherapy comprised two cycles of 5-fluorouracil at 700 mg/m<sup>2</sup>/day administered on days 1–4 as continuous intravenous infusion and nedaplatin (100 mg/m<sup>2</sup> administered i.v. over 2 h) given after the administration of 5-fluorouracil on day 1, repeated every 3 weeks, followed by intensity-modulated radiotherapy concurrent with nedaplatin. During intensity-modulated radiotherapy, nedaplatin was administered at a dose of 100 mg/m<sup>2</sup> intravenous infusion on days 1, 22 and 43, given ~60 min before radiation.

### **Results**

Fifty-nine (95.8%) of the 60 patients were assessable for response. Thirty-eight cases of complete response and 14 cases of partial response were confirmed after completion of chemoradiation, with the objective response rate of 86.7% (95% CI, 78.1–95.3%). The median follow-up period was 48 months (range, 30–62 months). The 3-year progression-free survival and overall survival were 75.0% (95% CI, 63.0–87.0%) and 85.5% (95% CI, 75.9–95.1%). No patient showed Grade 3 or higher renal dysfunction. The most commonly observed late effect was xerostomia, but the severity diminished over time, and the detectable xerostomia at 24 months was 10.2%. There were no treatment-related deaths during this study.

### **Conclusions**

Neoadjuvant chemotherapy with nedaplatin and 5-fluorouracil followed by concomitant nedaplatin and intensity-modulated radiotherapy is an effective and safe treatment for Southern China patients affected by locoregionally advanced nasopharyngeal carcinoma.

## **Efficacy and Feasibility of Combination Chemotherapy with S-1 and Cisplatin (2 Weeks Regimen) for Advanced Gastric Cancer**

## Objective

Although combination chemotherapy with 3 weeks of S-1 and cisplatin is effective for advanced gastric cancer, the toxicities of S-1 which mostly occur during the third week of administration are a major problem. To achieve fewer adverse effects with S-1 and higher dose intensity of cisplatin, we performed combination chemotherapy with 2 weeks of S-1 and cisplatin as first line. The aim of this retrospective study was to analyse the efficacy and feasibility of this regimen.

## Methods

S-1 (40–60 mg depending on patient's body surface area) was given orally twice daily for 2 consecutive weeks, and 70 mg/m<sup>2</sup> cisplatin was given intravenously on day 8, followed by a 2-week rest period.

## Results

Forty-eight patients received a total of 184 courses of chemotherapy. Overall response rate was 40.6% and median survival time was 411 days. Dose intensities were 257.6 mg/m<sup>2</sup>/week for S-1 and 16.4 mg/m<sup>2</sup>/week for cisplatin. The incidences of grade 3/4 haematological toxicities were leucopenia (19%), neutropenia (29%) and anaemia (17%), and those of grade 3 non-haematological toxicities were anorexia (31%) and nausea (21%). The rate of treatment discontinuation owing to toxicity was 10%.

## Conclusions

This regimen may be effective as an alternative therapy to 3 weeks of S-1 and cisplatin to reduce the toxicity of chemotherapy for advanced gastric cancer.

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## **Radiation Pneumonitis Following Twice-daily Radiotherapy with Concurrent Carboplatin and Paclitaxel in Patients with Stage III Non-small-cell Lung Cancer**

### Objective

To examine the effects of dose–volume factors on the development of radiation pneumonitis in patients with non-small-cell lung cancer who received twice-daily radiotherapy concurrently with carboplatin and paclitaxel chemotherapy.

### Methods

Radiotherapy consisted of twice-daily fractionation of 1.2 Gy, to a total dose of 60 Gy. Weekly carboplatin and paclitaxel were used as a concurrent chemotherapy. Effects of radiotherapy parameters on the development of radiation pneumonitis were retrospectively analyzed.

### Results

Fourteen of 37 patients developed Grade 2 or worse ( $\geq$ G2) radiation pneumonitis. Grade 2 or worse radiation pneumonitis occurred in all 5 patients with V<sub>5</sub> >40%, all 4 patients with V<sub>10</sub> >35%, all 4 patients with V<sub>13</sub> >32%, 9 of 14 patients with V<sub>20</sub> >24% and 8 of 11 patients with V<sub>30</sub> >22%, whereas 9 of 32 patients with V<sub>5</sub>

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## **Cancer Trends in China**

Cancer is the leading death cause in urban China and the second one in rural China. Lung cancer is the most common cancer, followed by stomach cancer, liver cancer, esophageal cancer and colorectal cancer. Cancer Control Programs in China focus on prevention, early diagnosis and treatment. The prevention program includes an anti-smoking campaign and immunization against hepatitis B for infants and children under the age of 15. Screening for breast and cervix cancers is among efforts for the early detection and treatment.

Public education and the promotion of healthy lifestyles have been actively carried out.

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## **Health-related Quality of Life in Patients with Colorectal Cancer Who Receive Oral Uracil and Tegafur plus Leucovorin**

### **Objective**

Adjuvant chemotherapy with oral uracil/tegafur plus leucovorin has been acknowledged to be a standard treatment for Stage II or III cancer of the colon. The objective of the study was to examine the health-related quality of life during treatment in patients with colorectal cancer who receive oral uracil/tegafur plus leucovorin.

### **Methods**

Health-related quality of life was assessed at baseline (pre-treatment) and at 5-week intervals during treatment, using the European Organization for Research and Treatment of Cancer QLQ-C30 questionnaires. Health-related quality of life data for five courses of treatment were then analyzed longitudinally.

### **Results**

Ninety-four patients completed the baseline and post-treatment health-related quality of life assessments. The post-treatment assessments changed significantly from the baseline values and favored post-treatment for all the scales except cognitive function, dyspnea, insomnia, constipation and diarrhea. Role function and social function changed by 10 or more points considered clinically significant. Most of the scales in patients with Grade 0&ndash;1 toxicities were better than those with Grade 2&ndash;3 toxicities, but Grade 2&ndash;3 toxicities were not associated with post-treatment deteriorations in health-related quality of life. The development of Grade 3 toxicities negatively affected on the four scales at the next assessment, compared with Grade 1&ndash;2 toxicities.

### **Conclusions**

Overall health-related quality of life did not deteriorate during adjuvant chemotherapy with oral uracil/tegafur plus leucovorin in patients with colorectal cancer, despite the effect from surgical damage, whereas the development of Grade 3 toxicities negatively affected on short-term health-related quality of life. Further comparative studies are needed.

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## **Development of a Predicting Tool for Survival of Terminally Ill Cancer Patients**

## Objective

To develop a predicting tool for survival of terminally ill cancer patients.

## Methods

This prospective, multicenter study was composed of two cohorts of samples: development and test. In the development sample of terminally ill cancer patients, 32 candidate predictors were studied to develop a new tool, Japan Palliative Oncology Study-Prognostic Index using the Cox proportional hazard model. Then the test sample was studied to validate Japan Palliative Oncology Study-Prognostic Index and compared it with the conventional predicting tools, such as palliative prognostic score and simplified palliative prognostic index.

## Results

Five significant predictors, physician's clinical prediction of survival, consciousness, pleural effusion, white blood cell count and lymphocyte % were derived from the analysis of 201 patients, and Japan Palliative Oncology Study-Prognostic Index was developed using these predictors. It could divide patients into three risk groups: low (A), intermediate (B) and high (C). Median survival times for Groups A, B and C were 51, 35 and 16 days, respectively. Survival probability for more than 30 days for Groups A, B and C in the development sample was 78%, 61% and 16%, respectively. Japan Palliative Oncology Study-Prognostic Index was studied in subsequent 208 patients for the test sample, and constant results (median survival times for Groups A, B and C; 67, 31 and 10 days, and survival probability for more than 30 days for Groups A, B and C; 81, 48 and 11%) were obtained. Palliative prognostic score can also predict three risk groups well, but simplified palliative prognostic index could not discriminate low risk from intermediate risk group.

## Conclusion

Japan Palliative Oncology Study-Prognostic Index, a tool to predict survival, has been developed. Its reliability should be confirmed further in the future study, comparing with palliative prognostic score.

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## Clinical Significance of Prostate Stem Cell Antigen Expression in Non-small Cell Lung Cancer

### Objective

Prostate stem cell antigen was originally identified as an overexpressed gene in prostate cancer and its overexpression correlated with disease progression and prognosis. In this study, we investigated the clinical significance and therapeutic potential of prostate stem cell antigen expression in non-small cell lung cancer.

### Methods

Prostate stem cell antigen expression was examined by immunohistochemistry in 97 primary tumors and 21 metastatic lymph nodes from non-small cell lung cancer patients who underwent curative resection from January 2001 through March 2003. Therapeutic potential of targeting prostate stem cell antigen was further examined by small interfering RNA method using human lung cancer cell line (A549).

### Results

Prostate stem cell antigen protein expression was detected in 94 of 97 primary lesions (97%) and all metastatic lymph nodes. Prostate stem cell antigen expression intensity was positively correlated with advanced pathological T-factor and stage (T1 vs. T2&dash;4,  $P = 0.014$ ; Stage I vs. Stages II&dash;IV,  $P = 0.029$ , respectively). The prognosis of patients with low prostate stem cell antigen expression was significantly better than those with high prostate stem cell antigen expression (5-year disease-free survival rate; 90% vs. 53%,  $P = 0.001$ ). Finally, small interfering RNA-mediated knockdown of prostate stem cell antigen resulted in the inhibition of lung cancer cell growth.

### Conclusions

Prostate stem cell antigen is highly expressed in non-small cell lung cancer and may be functionally important for this fatal disease.

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## Drug Monitoring During FOLFOX6 Therapy in a Rectal Cancer Patient on Chronic Hemodialysis

Long-term hemodialysis is considered to be a significant risk factor for cancer, but little is known about the use of oxaliplatin in patients on chronic hemodialysis. A 58-year-old man on chronic hemodialysis was treated for unresectable rectal cancer with synchronous hepatic metastasis by FOLFOX6 therapy with therapeutic drug monitoring. Plasma levels of total platinum, ultrafiltrate (free) platinum and 5-fluorouracil were monitored from the start of oxaliplatin administration to 120 h after the end of oxaliplatin infusion. Pharmacokinetic data of free platinum showed a bimodal pattern, decreased rapidly during the first dialysis and subsequently rose until 48 h after oxaliplatin infusion. The free platinum area under the curve was 15.7–18.9 µg h/ml when 40 mg/m<sup>2</sup> of oxaliplatin was administered, which was comparable to the area under the curve at 85 mg/m<sup>2</sup> in patient with normal renal function. The total platinum level reached a peak immediately before dialysis and gradually decreased. The 5-fluorouracil level decreased rapidly after the start of dialysis and remained constant during the continuous infusion of 5-fluorouracil. Tumor response was judged to be stable disease for >6 months, and no peripheral neuropathy or other toxicity was observed even after 11 courses. FOLFOX6 therapy with reduced dose of oxaliplatin had been safely performed for >6 months without any severe toxicity. The serum levels of free platinum showed bimodal pattern, and this second peak increased the area under the curve of free platinum. This pattern seems to be unique in patients on hemodialysis.

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## Implications of Body Mass Index in Japanese Patients with Prostate Cancer Who Had Undergone Radical Prostatectomy

### Objective

To determine the association between obesity and prostate cancer in Japanese recurrence after primary treatment with radical prostatectomy.

### Methods

The subjects were 173 Japanese patients with prostate cancer who had been treated with radical prostatectomy at Chiba University Hospital between April 1997 and March 2007. Clinicopathological characteristics and biochemical recurrence outcomes after radical prostatectomy were compared between the three body mass index cohorts.

### Results

Mean body mass index was 23.4 kg/m<sup>2</sup> with a standard deviation of 2.4, and mean follow-up period was 37.4 months. Operative time was longer and estimated blood loss was much more in obese patients. Patients with pT3&ge; had significantly higher serum prostate-specific antigen, total cholesterol levels, Gleason's sum and positive of surgical margin than pT2 patients. Recurrence rate was significantly higher in the 26.5 kg/m<sup>2</sup> and hyperlipidemia groups in pT3&ge; patients.

### Conclusions

Obesity is an independent predictor of disease recurrence in Japanese patients with pT3&ge; prostate cancer who underwent radical prostatectomy. Obese patients who underwent radical prostatectomy require vigilant follow-up care.

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## Does Health Status Influence Intention Regarding Screening Mammography?

## Objective

We analyzed information surveyed from a community-based sample of Korean women older than 40 years of age to understand the relationships between health status and screening behavior.

## Methods

In a cross-sectional population-based study, a two-stage, geographically stratified household-based sampling design was used for assembly of a probability sample of women aged 40–69 years living in Gunpo in Korea, resulting in a total sample size of 503 women. The primary outcome variable for this analysis was the respondent's intention to obtain a mammogram. Predictor variables included health status and other factors known to influence the use of cancer screening, such as age, education, income, marital status and the presence of co-morbid illnesses. Health status was assessed by using the EuroQol (EQ-5D).

## Results

The median EQ visual analogue scale score was 75.0, ranging from 20 to 100. In bivariate analyses, the percentage of women reporting to have intention toward mammography use decreased with worsening health status. Women who had problems with mobility or anxiety/depression showed lower intention to undergo future screening mammography. Multivariate logistic regression confirmed that health status was significantly associated with intention toward mammography use. Anxiety or depression was an independent predictor of future screening mammography use.

## Conclusions

Health status is significantly associated with intention regarding screening mammography use. Physicians or other health professionals should be aware that health status is an important component for health promotion, and should pay more attention to clients' possible vulnerability in screening mammography use due to their poor health status.

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## **Survivin and Smac Gene Expressions but not Livin Are Predictors of Prognosis in Non-small Cell Lung Cancer Patients Treated with Adjuvant Chemotherapy Following Surgery**

## Objective

Survivin and livin, which are members of the inhibitor of apoptosis protein family, regulate both programmed cell death and proliferation. Second mitochondria-derived activator of caspase is thought to regulate apoptosis by antagonizing inhibitor of apoptosis protein. These gene expressions are regarded as prognostic markers in some malignancies. However, result in previous studies of the association of these gene expressions with prognosis of patients with non-small cell lung cancer remains contradictory.

## Methods

Survivin, livin and second mitochondria-derived activator of caspase mRNA was detected by semi-quantitative reverse transcriptase&mdash;polymerase chain reaction in surgical resected tumor specimen from 66 non-small cell lung patients who received adjuvant platinum-based chemotherapy.

## Results

Results showed that patients with survivin high expression had significantly shorter tumor-free survival ( $P = 0.012$ ) and overall survival ( $P = 0.007$ ) than those with survivin low expression. There was a significant association of second mitochondria-derived activator of caspase high expression in non-small cell lung cancer tissue with longer tumor-free survival ( $P = 0.021$ ) and overall survival ( $P = 0.0013$ ). However, livin mRNA expression level had no impact on the tumor-free survival and overall survival of the patients. In multivariate analyses, survivin mRNA high expression ( $P = 0.033$  and  $P = 0.024$ ) and advanced pathologic stage ( $P = 0.009$  and  $P = 0.008$ ) were the factors which independently predicted a worse tumor-free survival and overall survival.

## Conclusions

Our data suggest that assessment of survivin and second mitochondria-derived activator of caspase mRNA expression may be useful for predicting survival in non-small cell lung cancer patients receiving platinum-based chemotherapy after surgical resection and can provide valuable information for deciding better therapy strategy.

<http://jco.oxfordjournals.org/cgi/content/short/hyp165v1?rss=1>

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## **Cisplatin and Etoposide as First-line Chemotherapy for Poorly Differentiated Neuroendocrine Carcinoma of the Hepatobiliary Tract and Pancreas**

## Objective

The combination chemotherapy consisting of cisplatin and etoposide, one of the standard regimens for small cell lung cancer, has been widely used to treat extrapulmonary poorly differentiated neuroendocrine carcinomas. However, there were no prior reports limited to the hepatobiliary tract and pancreas as the primary sites.

## Methods

We reviewed the cases in our database from October 1995 to January 2009 and retrospectively examined the clinical data of patients, with unresectable or recurrent poorly differentiated neuroendocrine carcinoma arising from the hepatobiliary tract and pancreas, who received combination chemotherapy with cisplatin and etoposide as the first-line treatment. The chemotherapy regimen consisted of cisplatin 80 mg/m<sup>2</sup> given intravenously on day 1 and etoposide 100 mg/m<sup>2</sup> intravenously on days 1–3, repeated every 3–4 weeks.

## Results

Twenty-one patients were treated with the above regimen of cisplatin and etoposide combination chemotherapy. The primary tumor site was the liver in 2 patients, gallbladder in 8 patients, pancreas in 10 patients and ampulla of Vater in 1 patient. Although no complete responses were obtained, three patients had partial responses, resulting in an overall response rate of 14%. Median progression-free survival was 1.8 months, and median overall survival was 5.8 months. The major adverse events were myelosuppression and gastrointestinal toxicities, with Grade 3 or 4 neutropenia (90%), nausea (33%) and anorexia (24%).

## Conclusions

Cisplatin and etoposide combination as the first-line chemotherapy for hepatobiliary or pancreatic poorly differentiated neuroendocrine carcinoma had only marginal antitumor activity and relatively severe toxicity compared with previous studies on extrapulmonary poorly differentiated neuroendocrine carcinoma treated with the same regimen.

<http://jjco.oxfordjournals.org/cgi/content/short/hyp173v1?rss=1>

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## **Current Status and Problems in Development of Molecular Target Agents for Gastrointestinal Malignancy in Japan**

Since late 1990s, many molecular target agents have been introduced to clinical trials for various kinds of tumors, and some of them showing significant benefits have been approved. However, these global trials were mainly conducted outside Japan, and the 'drag lag' has been a serious problem in Japan recently. Nowadays, Japanese institutions have been participating in some global trials, and the drug lags are getting shorter. For colorectal cancer, molecular target agents such as bevacizumab and cetuximab have been approved in Japan, resulting in improved clinical outcomes. For gastric cancer, Japanese institutions not only contribute to the global Phase III trials of trastuzumab and bevacizumab but also show leadership in the early development of other new agents. For pancreatic cancer, only erlotinib has shown a survival benefit in these 10 years. Worldwide approach including Japan is warranted to achieve better clinical outcomes. For liver cancer, although Japanese institutions did not participate even in the Asian trial of sorafenib, it has been approved in Japan. For esophageal cancer, because there has been no new molecular target agents developed by pharmaceutical companies, investigator-initiated registration trial will play an important role. For all gastrointestinal malignancies, molecular target agents have made a progress in their treatments. In the near future, Japanese institutions will participate in more and more global trials and should play a specific role in worldwide drug development. Furthermore, the optimal use of these new drugs, molecular target agents, based on the daily practice should also be explored in Japan.

<http://jjco.oxfordjournals.org/cgi/content/short/hyp171v1?rss=1>

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## **Transdermal Fentanyl for Pain Caused by Radiotherapy in Head and Neck Cancer Patients Treated in an Outpatient Setting: A Multicenter Trial in Taiwan**

### **Objective**

This study evaluated the efficacy and safety of transdermal fentanyl in the outpatient treatment of head and neck cancer patients with pain caused by radiotherapy.

### **Methods**

Patients with a visual analogue scale score  $\geq 4$  were invited to participate in the study. The following variables were collected: visual analogue scale, the Brief Pain Inventory, concomitant pain medications and adverse effects. A total of 163 head and neck cancer patients were enrolled (148 males and 15 females; median age, 53 years; age range, 21–72 years). Seventy-two (44%) patients had a visual analogue scale score  $>6$  at enrollment, despite the use of non-steroidal anti-inflammatory drugs or weak opioids. Ninety-four (57.7%) patients received concurrent chemotherapy.

### **Results**

A total of 88 patients completed the study, whereas 55 underwent a drop-out by side effects. The most frequently reported adverse events were vomiting (23.9%) and nausea (16.6%). Treatment with transdermal fentanyl resulted in a significant decrease in visual analogue scale and Brief Pain Inventory scores that persisted during treatment. In the overall efficacy evaluation, the pain-alleviating effect, the easiness of application and the overall impression of transdermal fentanyl were rated as good by 54.5%, 65.9% and 59.1% of the completers, respectively. Effects of transdermal fentanyl were rated as good by 64.8% of the investigators.

### **Conclusions**

Our data provide evidence that transdermal fentanyl is effective and relatively easy to use for outpatient treatment of pain control in head and neck cancer patients following radiotherapy in selected patients. Reduction of side effects and effective pain management need to be paramount in the management of head and neck cancer patients undergoing radiotherapy.

<http://jjco.oxfordjournals.org/cgi/content/short/hyp166v1?rss=1>

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## **Extraperitoneal Approach Induces Postoperative Inguinal Hernia Compared with Transperitoneal Approach after Laparoscopic Radical Prostatectomy**

## Objective

The aim of this study was to determine the incidence and risk factors of postoperative inguinal hernia and to investigate whether the difference of approach could induce postoperative inguinal hernia after laparoscopic radical prostatectomy.

## Methods

We reviewed 493 consecutive patients who underwent laparoscopic radical prostatectomy from November 2000 to November 2007, and evaluated various preoperative parameters, specifically age, prostate-specific antigen (ng/ml), body mass index (kg/m<sup>2</sup>), prostate volume (ml), previous major abdominal surgery, previous appendectomy, previous inguinal hernia repair and laparoscopic approach as risk factors for postoperative inguinal hernia.

## Results

Inguinal hernia occurred in 4 (4.9%) of the 81 patients in the transperitoneal approach group, and in 37 (9.0%) of the 412 patients in the extraperitoneal approach group. The overall incidence of inguinal hernia was 8.3% (41 of 493 patients). The median inguinal hernia-free survival time was 35 months and 6 months in the transperitoneal approach and extraperitoneal approach groups, respectively. Inguinal hernia developed within 2 years after surgery in 2 (50%) of 4 patients in the transperitoneal approach group, in 34 (91.9%) of 37 patients in the extraperitoneal approach group, for a total of 36 (87.8%) of 41 patients overall. Multivariate analysis showed that the extraperitoneal approach was a significant risk factor ( $P = 0.043$ ) for inguinal hernia.

## Conclusions

Inguinal hernia is a frequent complication after laparoscopic radical prostatectomy, and the incidence of inguinal hernia is greater with the extraperitoneal approach than with the transperitoneal approach.

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## **A Case with Hodgkin Lymphoma and Front-temporal Lobular Degeneration (FTLD)-like Dementia Facilitated by Chemotherapy**

We report a case of a 39-year-old man with Hodgkin lymphoma who developed depressive symptoms after starting adriamycin, bleomycin, vinblastine and dacarbazine chemotherapy and later exhibited sexual disinhibition in addition to cognitive dysfunction (mainly executive dysfunction). Seven months after the start of adriamycin, bleomycin, vinblastine and dacarbazine chemotherapy, he was finally diagnosed as having front-temporal lobular degeneration-like dementia facilitated by adriamycin, bleomycin, vinblastine and dacarbazine chemotherapy. At the time of writing, the patient's condition has persisted for more than 6 months after the discontinuation of adriamycin, bleomycin, vinblastine and dacarbazine chemotherapy, and the changes in brain function brought on by the adriamycin, bleomycin, vinblastine and dacarbazine chemotherapy may now be irreversible. This case points to the importance of being attentive to the appearance of neuropsychiatric symptoms and evaluating brain functions properly when performing anti-cancer chemotherapy.

<http://jjco.oxfordjournals.org/cgi/content/short/hyp170v1?rss=1>

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## **A Randomized, Double-blind, Parallel, Comparative Study to Evaluate the Efficacy and Safety of Ramosetron plus Dexamethasone Injection for the Prevention of Acute Chemotherapy-induced Nausea and Vomiting**

## Objective

To evaluate the efficacy of intravenous ramosetron plus dexamethasone for the prevention of acute chemotherapy-induced nausea and vomiting.

## Methods

Cancer patients scheduled to receive chemotherapy containing either of the four drugs (cisplatin, doxorubicin, epirubicin or oxaliplatin) were enrolled. They were randomized to receive intravenous ramosetron 0.3 mg plus dexamethasone 20 mg or granisetron 3 mg plus dexamethasone 20 mg 30 min before chemotherapy on day 1. The primary efficacy parameter is complete response rate, which was defined by the proportion of patients without vomiting and no requirement for rescue drugs within 24 h after chemotherapy.

## Results

A total of 285 patients were enrolled. The primary efficacy analysis included 274 patients. The complete response rate was 77.37% in the ramosetron 0.3 mg plus dexamethasone 20 mg group (137 patients) and 81.75% in the granisetron 3 mg plus dexamethasone 20 mg group (137 patients) with a difference of &ndash;4.38% (95% confidence interval: &ndash;14.64, 5.89). Therefore, non-inferiority of ramosetron 0.3 mg plus dexamethasone 20 mg to granisetron 3 mg plus dexamethasone 20 mg was demonstrated with non-inferiority margin &ndash;15%. For patients treated with cisplatin, non-inferiority of ramosetron 0.3 mg plus dexamethasone 20 mg to granisetron 3 mg plus dexamethasone 20 mg could not be demonstrated. Only a few patients required rescue medications, 7.3% in the ramosetron 0.3 mg plus dexamethasone 20 mg group and 5.1% in the granisetron 3 mg plus dexamethasone 20 mg group ( $P = 0.44$ ). All 285 patients were included for safety analysis; 36.11% (52/144) and 23.40% (33/141) experienced at least one adverse event within 24 h in the ramosetron 0.3 mg plus dexamethasone 20 mg and granisetron 3 mg plus dexamethasone 20 mg groups, respectively. Four ramosetron-related adverse events among 144 patients were observed including two moderate elevation of liver enzymes and one each of mild hiccup and moderate skin rash.

## Conclusions

The combination of ramosetron plus dexamethasone was an effective treatment to prevent acute chemotherapy-induced nausea and vomiting.

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## **Successful Management by Provocative Angiography and Endovascular Stent of Ureteroarterial Fistula in a Patient with a Long-term Indwelling Ureteral Stent**

We present the clinical course of a ureteroiliac arterial fistula in a patient who had been managed by ureteral stenting for 8 years for severe ureteral stricture after abdominoperineal resection with pelvic irradiation for advanced rectal cancer. A multidisciplinary team approach including provocative angiography and an endovascular stent saved the life of the patient. Ureteroarterial fistula is a rare complication of a long-term indwelling ureteral stent that is potentially fatal unless a prompt diagnosis and adequate therapy are provided. Heightened awareness and a high index of suspicion for this condition are required to make an early diagnosis.

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## **Tumor Multiplicity is an Independent Prognostic Factor of Non-muscle-invasive High-grade (T1G3) Bladder Cancer**

## Objective

Non-muscle-invasive high-grade (T1G3) bladder cancers have high potential for progression. The objective of this study is to clarify the clinicopathological factors affecting the outcome of T1G3 bladder cancer.

## Methods

We retrospectively reviewed 60 cases of T1G3 bladder cancer between 1994 and 2006. The correlations of both intravesical recurrence and progression with prognostic factors, such as T stage, history of bladder cancer, multiplicity, concomitant carcinoma in situ, tumor size, intravesical instillation of bacillus Calmette&ndash;Guérin and intravesical chemotherapy, were evaluated by multivariate analysis with the Cox proportional hazards model.

## Results

Median follow-up period was 52 months (4&ndash;105 months). Thirty-seven cases of intravesical recurrence (61.7%) were observed during follow-up. Two- and 5-year recurrence-free survival rates were 44.1% and 36.1%, respectively. Tumor multiplicity and instillation of bacillus Calmette&ndash;Guérin were significantly correlated with intravesical recurrence on multivariate analysis. Ten cases of progression (16.7%) were observed during the follow-up period. Two- and 5-year progression-free survival rates were 87.7% and 83.4%, respectively. Only tumor multiplicity was significantly correlated with progression on multivariate analysis.

## Conclusions

T1G3 cancers with multiple lesions showed high risks of intravesical recurrence and progression. Although bacillus Calmette&ndash;Guérin instillation reduced the risk of intravesical recurrence, no effect was observed on disease progression.

<http://jjco.oxfordjournals.org/cgi/content/short/hyp159v1?rss=1>

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## Primitive Neuroectodermal Tumor of the Liver: A Case Report

Ewing sarcoma/primitive neuroectodermal tumor is a rare tumor of soft tissues of thoraco-pulmonary regions, pelvis and lower extremities. Involvement of visceral organs by primitive neuroectodermal tumor is even rarer, with the kidney being the most commonly involved organ. Involvement of the liver has been reported in the form of metastasis from other primary sources presenting as liver abscess. We report a 20-year-old lady presenting with massive hepatomegaly, with computed tomography scan evidence of diffuse hepatomegaly and a normal porta and intrahepatic biliary radicles. She subsequently underwent ultrasonography-guided true-cut needle biopsy of the liver. Histopathology of the liver revealed nests of small round blue tumor cells in the background of hepatocytes infiltrating the liver, which expressed Mic-2 and Fli-1, and were negative for cytokeratin, desmin, hepatocyte-specific antigen (OCHIE5), synaptophysin, chromogranin A and CD-20. Immunohistochemistry revealed CD-99-positive. Extensive search regarding any possible different site of involvement by the tumor was negative. The patient responded to a combination therapy of vincristine, adriamycin and cyclophosphamide alternating with ifosfamide and etoposide 3 weekly over 43 weeks and has been doing well even after 1 year of diagnosis. The clinical presentation, the macroscopic aspect, together with the histological pattern, the cytological characteristic and the cellular immunophenotype lead to the diagnosis of primary primitive neuroectodermal tumor of the liver which responded well to combination chemotherapy.

<http://jjco.oxfordjournals.org/cgi/content/short/hyp158v1?rss=1>

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## Clinical Safety and Feasibility of a Newly Developed, Simple Algorithm for Decision-making on Neurovascular Bundle Preservation in Radical Prostatectomy

## Objective

We investigated the clinical safety and feasibility of an algorithm we developed for the decision-making on neurovascular bundle preservation in radical prostatectomy to decrease the incidence of positive surgical margins.

## Methods

We prospectively applied our algorithm to 82 patients (164 prostate sides) with clinically localized prostate cancer who underwent radical prostatectomy at our institution between October 2004 and September 2006. The algorithm was developed using the apical core characteristics, clinical T stage, preoperative prostate-specific antigen level and Gleason sum. All prostate sides were divided into two groups by the algorithm: 115 sides (70.1%) were qualified for neurovascular bundle preservation (favorable algorithm side group) and 49 sides (29.9%) for non-neurovascular bundle preservation (unfavorable algorithm side group).

## Results

Median patient age was 66 years (range: 52–77) and median prostate-specific antigen was 7.1 ng/ml (range: 1.4–29.6). Overall, a positive surgical margin was observed in 23 sides (14.0%). The incidence of positive surgical margins at the apex was significantly correlated with the maximal diameter of the tumor in the apex (P

## Conclusions

This simple algorithm is safe and feasible for the decision-making on neurovascular bundle preservation from the aspect of cancer control in radical prostatectomy patients.

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## **Case Series of Cetuximab Monotherapy for Patients with Pre-treated Colorectal Cancer Complicated with Hyperbilirubinemia due to Severe Liver Metastasis**

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## **Disturbance of the Growth Hormone-Insulin-like Growth Factor-1 Axis Associated with Poor Performance Status in Patients with Solid Tumors**

### Objective

Hormonal imbalance characterized by excessive production of growth hormone (GH) and a low circulating concentration of insulin-like growth factor (IGF)-1 has been demonstrated in individuals with various serious conditions. However, little is known about changes in the GH–IGF-1 axis in cancer patients.

### Methods

We prospectively examined the circulating levels of several hormones in 58 patients with solid tumors who were classified according to Eastern Cooperative Oncology Group performance status (PS): PS 0–1, n = 15; PS 2, n = 15; PS 3, n = 15; and PS 4, n = 13. The relations of hormone concentrations, with a focus on the GH–IGF-1 system, to PS were evaluated by Spearman's rank correlation test and regression analysis.

### Results

The circulating levels of IGF-1, IGF-binding protein-3 and thyroid hormones (total T3 and T4) were inversely correlated with PS score. The concentration of GH was increased irrespective of PS but not statistically significant. The ratio of IGF-I to GH was inversely correlated with PS. The levels of GH and IGF-1 in all patients were also inversely correlated.

### Conclusions

The present study suggests that the GH–IGF-1 axis is disturbed in patients with cancer.

## **Phase I/II Study of S-1 plus Cisplatin Combination Chemotherapy in Patients with Advanced/Recurrent Head and Neck Cancer**

### **Objective**

The objectives of this study were to determine the maximum tolerated dose (MTD) and recommended dose (RD) of S-1 plus cisplatin (CDDP) and to evaluate safety and efficacy using the defined RD in advanced/recurrent head and neck cancer (HNC).

### **Methods**

S-1 was administered orally at 40 mg/m<sup>2</sup> twice daily for 14 consecutive days, and CDDP was infused on day 8 at a dose of 60 and 70 mg/m<sup>2</sup>. Each course was repeated every 4 weeks.

### **Results**

A total of 38 patients were registered, 10 patients for the Phase I study and an additional 28 patients for the Phase II study. Although no dose-limiting toxicity (DLT) was observed in the CDDP 60 mg/m<sup>2</sup> (Level 1) group, two of six patients in the CDDP 70 mg/m<sup>2</sup> (Level 2) group exhibited DLT (fatigue/diarrhea). The MTD was not achieved in the Phase I study. Level 2 was therefore determined as the RD. In the Phase II study, 34 patients, including 6 patients from the Phase I study, were evaluated. At the termination of treatment, the confirmed response rate was 44.1% (15/34, 95% CI: 27.4–60.8). The best response rate without an adequate duration time was 67.6% (95% CI: 51.9–83.4). The median survival period was 16.7 months, and the 1-year survival rate was 60.1%. The main toxicities of Grade 3 or above were anorexia (26.5%), nausea (14.7%), neutropenia/thrombocytopenia (11.8%) and anemia/fatigue (8.8%).

### **Conclusions**

This is considered to be an effective regimen with acceptable toxicities for HNC.

## **A Phase III Randomized Trial of Lobectomy Versus Limited Resection for Small-sized Peripheral Non-small Cell Lung Cancer (JCOG0802/WJOG4607L)**

A Phase III study was started in Japan to evaluate the non-inferiority in overall survival of segmentectomy compared with lobectomy in patients with small-sized (diameter ≤2 cm) peripheral non-small cell lung cancer, excluding radiologically determined non-invasive cancer. This study began in August 2009, and a total of 1100 patients will be accrued from 71 institutions within 3 years. The primary endpoint is overall survival. The secondary endpoints are post-operative respiratory function, relapse-free survival, proportion of local recurrence, adverse events, proportion of patients who complete segmentectomy, duration of hospitalization, duration of chest tube placement, operation time, blood loss and number of auto-sutures used. This study is one of the first intergroup studies in Japan between the Japan Clinical Oncology Group and the West Japan Oncology Group.

## **Increased Survivin mRNA in Malignant Pleural Effusion is Significantly Correlated with Survival**

## Objective

The sensitivity of cytologic examination of pleural effusions is variable and not predictive of prognosis. Survivin is an inhibitor of apoptosis that may be a novel diagnostic/prognostic marker of cancers. This study aimed to determine the diagnostic and prognostic value of measuring survivin mRNA levels in pleural effusions.

## Methods

Eighty-eight consecutive pleural effusion samples were examined for both cytology and survivin mRNA level. The accuracy of diagnosis and the correlation between survivin mRNA level and survival in malignant pleural effusion (MPE) were determined. Pleural effusions were divided into three groups: Group I, malignancy-associated (n = 44); Group II, inflammatory (n = 27); and Group III, transudative (n = 17).

## Results

Survivin mRNA levels in Group I ( $1.03 \pm 0.61$ , range 0–2.96) were significantly higher than those in Groups II ( $0.45 \pm 0.69$ , range 0–3.30) and III ( $0.08 \pm 0.22$ , range 0–0.71) (P < 0.05). Conclusions: Survivin mRNA level is significantly higher in MPEs. Over-expression of survivin mRNA correlates with poor prognosis in cancer patients.

<http://jjco.oxfordjournals.org/cgi/content/short/hyp151v1?rss=1>

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## Primary Urothelial Carcinoma of the Upper Urinary Tract in Dialysis Patients with 5-year Follow-up

### Objective

In this study, we assessed the clinical and pathological characteristics of urothelial cancers of the upper urinary tract (UUT) in patient under dialysis and evaluated the efficacy and complications of surgical management of the disease.

### Methods

A total of 70 dialysis patients with primary urothelial carcinoma (UC) of the UUT were identified with 5-year follow-up after surgery (61–122 months). Potential factors were analysed to determine the risk factors of subsequent tumours and unfavourable prognostic factors of overall survival. Incidence of urothelial tumours and overall survival of 7503 dialysis patients were also evaluated.

### Results

The incidence of primary UC of the UUT in dialysis patients in Taiwan was 0.93%. The 2-year and 5-year overall survival rates of dialysis patients with primary UC of the UUT were 74.3% and 42.9%, respectively. Subsequent bladder tumours and contralateral UUT tumours developed in 52.6% and 37.9% patients, respectively. No significant risk factor could be identified to predict subsequent tumours in dialysis patients. Pathological stage (P = 0.021) and grade (P < 0.05) were significantly associated with overall survival.

Conclusions: Closely monitoring the residual urinary tracts after nephroureterectomy in dialysis patients with primary UC of the UUT should be performed. There is no statistical difference for overall survival between one-stage and two-stage bilateral nephroureterectomy.

<http://jjco.oxfordjournals.org/cgi/content/short/hyp143v1?rss=1>

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## CK7, CK20, CDX2 and MUC2 Immunohistochemical Staining Used To Distinguish Metastatic Colorectal Carcinoma Involving Ovary from Primary Ovarian Mucinous Adenocarcinoma

## Objective

Colorectal adenocarcinoma, the most common tumor that metastasizes to the ovary, is often difficult to distinguish from primary ovarian mucinous adenocarcinoma (POMA). Obtaining the correct diagnosis is difficult but crucial to treatment and prognosis.

## Methods

We evaluated the immunohistochemical (IHC) expression of cytokeratin 7 (CK7), cytokeratin 20 (CK20), CDX2, CEA, MUC2, MUC5AC and -methylacyl-CoA racemase (AMACR) in 22 POMAs and 41 metastatic colorectal adenocarcinomas (MCAOs) involving ovaries.

## Results

MCAOs, in contrast with POMAs, were almost always negative for MUC5 (97.6%), often negative for CK7 (82.9%), focal or diffuse positive for CDX2 (73.2%), diffuse positive for CK20 (65.9%), focal or diffuse positive for MUC2 (51.2%), diffuse positive for CEA (41.5%) and negative for AMACR (41.5%). We therefore considered CK7 (–), CK20 (diffuse +), CDX2 (+) and MUC2 (+) to be colonic markers and regarded cases with expression of more than two colonic markers as MCAO, those with no expression of colonic markers as POMA and those with expression of one colonic marker as indeterminate. Using CK7/CK20/CDX2/MUC2, 82.5% of the cases were correctly classified, 6.3% were misclassified and 6.3% were indeterminate.

## Conclusion

CK7, CK20, CDX2 and MUC2 IHC staining is a useful adjunctive diagnostic tool to differentiate MCAOs from POMAs, in addition to clinical history and gross and microscopic findings.

<http://jjco.oxfordjournals.org/cgi/content/short/hyp150v1?rss=1>

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## **A Phase II Study of Sunitinib in Japanese Patients with Metastatic Renal Cell Carcinoma: Insights into the Treatment, Efficacy and Safety**

### Objective

This study aims to assess the efficacy and safety of sunitinib in Japanese patients with metastatic renal cell carcinoma (RCC).

### Methods

Fifty-one Japanese patients with prior nephrectomy, 25 treatment-naïve patients (first-line group) and 26 cytokine-refractory patients (pretreated group) were enrolled in this phase II trial. Patients received sunitinib 50 mg orally, once daily, in repeated 6-week cycles (4 weeks on treatment, 2 weeks off). The primary endpoint was RECIST-defined objective response rate (ORR) with tumour assessments every 6 weeks via computed tomography or magnetic resonance imaging. Toxicity was assessed regularly. In the primary efficacy analysis of the intent-to-treat (ITT) population, ORR and 95% confidence interval were calculated based on independent review. Secondary time-to-event endpoints, such as progression-free survival (PFS), were estimated using the Kaplan&ndash;Meier method.

### Results

In the ITT population, ORR was 48.0% in the first-line group (after a median 4 cycles), 46.2% in the pretreated group (5 cycles) and 47.1% overall, with median times to tumour response of 7.1, 10.7 and 10.0 weeks, respectively. Median PFS was 46.0, 33.6 and 46.0 weeks, respectively. The most common treatment-related grade 3/4 adverse events and laboratory abnormalities were fatigue (20%), hand-foot syndrome (14%) and hypertension (12%), decreased platelet count (55%), decreased neutrophil count (51%), increased lipase (39%) and decreased lymphocyte count (33%).

### Conclusions

In Japanese patients with RCC, sunitinib is consistently effective and tolerable with similar risk/benefit as that in Western patients, though there was a trend toward greater antitumour efficacy and higher incidence of haematological adverse events in Japanese patients.

## **Massive Hematuria from the Bilateral Upper Urinary Tract in a Patient Treated for Advanced Lung Cancer with Gefitinib**

We report a case of gefitinib-induced bilateral upper urinary tract bleeding in an 82-year-old woman administered the drug daily for advanced non-small cell adenocarcinoma of the lung (T4N3M0). Hematuria is an uncommon adverse effect of gefitinib, and in most cases, the bleeding site is unknown. On the 44th day of oral gefitinib administration, the patient noted asymptomatic macroscopic bloody urine. Cystoscopy revealed bleeding from the bilateral ureteric orifices without hemorrhagic inflammation of the bladder. One week later, she was admitted complaining of severe abdominal pain, and her condition was found to be complicated by liver damage and renal dysfunction. We stopped gefitinib administration and started hydration and diuresis. Renal function and urine output soon recovered, and at the request of the patient, we restarted gefitinib, administering it every other day, which was sufficient to maintain antitumor activity and stabilize the disease. On the 41st day after restarting gefitinib, hematuria and proteinuria reappeared. We therefore stopped the gefitinib, and the patient was followed with supportive care. The patient's autopsy findings denied organic urologic diseases. Instead, the reproducibility of the hematuria from the upper urinary system strongly suggests an unexpected gefitinib-related adverse effect.

<http://jjco.oxfordjournals.org/cgi/content/short/hyp141v1?rss=1>

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## **Role of Pelvic Lymph Node Dissection in Lymph Node-Negative Patients with Invasive Bladder Cancer**

### **Objectives**

The role of pelvic lymphadenectomy in patients with lymph node-negative bladder cancer at radical cystectomy (RC) has not yet been examined in detail. We retrospectively reviewed patients who underwent RC with pelvic lymphadenectomy for bladder cancer from January 1987 to March 2008.

### **Methods**

We identified consecutive data on 169 patients who underwent RC for bladder cancer. The mean follow-up was 64 months (range: 1–253 months). Node-positive status (pN(+)) was seen in 16 patients and 91 were diagnosed as node-negative (pN(–)). The lymph node status of the remaining 62 patients was unclear (pN(x)). We analysed the association between lymph node status and cancer-specific survival (CSS), and examined the role of the number of retrieved lymph nodes, particularly in pN(–).

### **Results**

The median number of retrieved nodes was 12.9 and 10.2 for stage pN(+) and stage pN(–), respectively. In 91 patients with pN(–), multivariate analysis revealed that pathological T3-4 (P = 0.0276) and less than nine retrieved lymph nodes (P = 0.0108) were independent risk factors for CSS. In a subgroup of 83 patients with pT3-4, Kaplan–Meier curves showed that the 5-year CSS rate in pN(–) patients with less than nine retrieved lymph nodes was 38.8%, which was extremely similar to the 40.8% in pN(+) and 45.1% in pN(x).

### **Conclusions**

Our results demonstrate that at least nine lymph nodes should be removed to improve the survival of pN(–) patients at RC and lymphadenectomy, and would provide information not only on prognosis but also on the therapeutic impact on pT3-4 invasive bladder cancer.

<http://jjco.oxfordjournals.org/cgi/content/short/hyp147v1?rss=1>

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## **Capecitabine Monotherapy is Efficient and Safe in All Line Settings in Patients with Metastatic and Advanced Breast Cancer**

### **Objective**

Capecitabine is effective and well tolerated in patients with anthracycline- and/or taxane-pre-treated metastatic breast cancer. We compared the efficacy and safety of capecitabine monotherapy between 1st, 2nd, 3rd and  $\geq$ 4th line settings for advanced and metastatic breast cancer pre-treated with/without anthracycline and taxanes.

### **Methods**

Subjects comprised 84 patients with histologically confirmed advanced or metastatic breast cancer and at least one measurable metastatic lesion. We evaluated time to disease progression (TTP), response rate (RR) and clinical benefit rate (CBR) for 1st (n = 17), 2nd (n = 28), 3rd (n = 23) and  $\geq$ 4th (n = 16) line setting treatments of capecitabine monotherapy.

### **Results**

Median number of cycles of capecitabine monotherapy was 12 cycles in 1st line, 11 cycles in 2nd line, 9 cycles in 3rd line and 11 cycles in  $\geq$ 4th line. RR and CBR were 23.5% and 58.8% in 1st line, 21.4% and 53.6% in 2nd line, 21.7% and 52.2% in 3rd line, and 18.8% and 50.0% in  $\geq$ 4th line, respectively. No significant differences in TTP were seen between each line setting (P = 0.843).

### **Conclusions**

Capecitabine monotherapy is effective and well tolerated in all line settings of chemotherapy in patients with metastatic or advanced breast cancer, and is suitable for outpatient therapy.

<http://jjco.oxfordjournals.org/cgi/content/short/hyp145v1?rss=1>

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## **Can Vaginal Misoprostol Effectively Increase Rate of a Satisfactory Colposcopy? A Randomized Double-blind Placebo-controlled Trial**

### **Objective**

To evaluate the effectiveness of vaginal misoprostol in overcoming an unsatisfactory colposcopy in the patients who had abnormal cervical cytology and to evaluate side effects of vaginal misoprostol.

### **Methods**

Sixty patients with an unsatisfactory colposcopy during the period of September 2007–November 2008 were recruited and randomly allocated to receive either two tablets of 200  $\mu$ g misoprostol (400  $\mu$ g) or two tablets of similar-looking placebo vaginally. Colposcopic re-examination was performed ~6 h later. The results and side effects before and 2 weeks after the colposcopic re-examination were recorded.

### **Results**

Six out of 30 patients in the misoprostol group (20.0%) had a satisfactory colposcopic re-examination compared with 2 out of 27 patients (7.4%) in the placebo group without statistically significant difference (P = 0.172). Three patients in the placebo group dropped out due to not present at the appointment time. Six out of 30 patients (20.0%) and 1 out of 30 patients (3.3%) in the misoprostol group had side effects before and 2 weeks after the colposcopic re-examination orderly. Twenty-seven patients in the placebo group did not have any side effects before and 2 weeks after the colposcopic re-examination. All side effects occurred were minimal and well tolerated.

### **Conclusions**

Four hundred micrograms of vaginal misoprostol were not proved to be effective in converting an unsatisfactory to a satisfactory colposcopy.

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