The 12th
Aichi Cancer Center
International Symposium

Perspective of Oncological Strategy
for Gastrointestinal Cancer

Organizing Committee of the 12th Aichi Cancer Center International Symposium
Yasuo Morishima (Chairperson)
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President of Aichi Cancer Center: Toshitada Takahashi

January 13, 2007
Aichi Cancer Center, Nagoya, Japan
PROGRAM OF SYMPOSIUM

9:30-9:35 Opening Remarks: Toshitada Takahashi

Basic Research and Preclinical Study on Cancer Therapeutics

Chairperson: Takashi Joh (Nagoya City University)
Masae Tatematsu (Aichi Cancer Center Research Institute)

9:35-10:10 Jean-Pierre Issa (MD Anderson Cancer Center, USA)
Integrated genetic and epigenetic analysis identifies colon cancer as three different diseases

10:10-10:40 Toshikazu Ushijima (National Cancer Center Research Institute)
DNA methylation as a marker for the past and future

10:40-11:05 Hayao Nakanishi (Aichi Cancer Center Research Institute)
HER family as potential molecular targets for anti-cancer therapy against gastrointestinal malignancies

Development of Chemotherapy for Pancreatic Cancer

Chairperson: Akimasa Nakao (Nagoya University)
Kenji Yamao (Aichi Cancer Center Hospital)

11:05-11:40 Malcolm J. Moore (Princess Margaret Hospital, Canada)
Perspectives in pancreatic cancer chemotherapy

11:40-12:10 Takuji Okusaka (National Cancer Center Hospital)
Treatment of pancreatic cancer: challenges in Japan

12:10-12:35 Akira Sawaki (Aichi Cancer Center Hospital)
The future direction of chemotherapy for pancreatic cancer

12:35-13:40 Lunch
### Chemoradiotherapy for Head & Neck and Esophageal Cancers

**Chairperson:** Soji Ozawa (Fujita Health University)  
Nobukazu Fuwa (Aichi Cancer Center Hospital)

**13:40-14:40** Carol R. Bradford (University of Michigan, USA)  
Current thoughts on the role of chemotherapy and radiation in advanced head and neck cancer

Tetsuya Ogawa (Aichi Cancer Center Hospital)  
Prediction of chemosensitivity for head and neck cancer

**14:40-15:10** Satoshi Ishikura (National Cancer Center Hospital)  

**15:10-15:35** Kei Muro (Aichi Cancer Center Hospital)  
Definitive chemoradiotherapy for stage I-III esophageal squamous cell carcinoma: Current results in Japan.

**15:35-16:00** Coffee Break

### Chemotherapy for Colorectal Cancer

**Chairperson:** Hiroya Takiuchi (Osaka Medical College)  
Tomoyuki Kato (Aichi Cancer Center Hospital)

**16:00-16:35** Claus-Henning Köhne (Klinikum Oldenburg, Germany)  
Systemic chemotherapy for colorectal cancer

**16:35-17:05** Atsushi Ohtsu (National Cancer Center Hospital East)  

**17:05-17:30** Yoshitaka Inaba (Aichi Cancer Center Hospital)  
Hepatic arterial infusion chemotherapy for liver metastasis from colorectal cancer

**17:30-17:35** Concluding Remarks: Yasuo Morishima
Welcome Remarks

Toshitada Takahashi
President, Aichi Cancer Center

On behalf of the organizing committee, I am pleased to welcome you to the 12th Aichi Cancer Center International Symposium. My special thanks are to the speakers, chairpersons and participants who have traveled a long distance to join us here in Nagoya.

Our first international symposium was held in 1994 when Aichi Cancer Center celebrated its 30th anniversary and the International Conference Center was newly built. Since then the symposium has been held annually, and the organizing committee has selected timely topics on basic research, translational research, prevention, diagnosis and treatment on cancer.

The main theme of this year’s symposium is “Perspective of Oncological Strategy for Gastrointestinal Cancer”. This topic was selected since considerable progress has been made in this field in recent years. The symposium consists of 4 sessions; the first session is “Basic Research and Preclinical Study on Cancer Therapeutics”, the second is “Development of Chemotherapy for Pancreatic Cancer”, the third is “Chemoradiotherapy for Head & Neck and Esophageal Cancers” and the fourth is “Chemotherapy for Colorectal Cancer”.

I sincerely hope that this meeting will be an excellent opportunity to learn the current status and future perspectives in cancer of digestive organs. I also wish that this symposium will contribute toward the victory in the war against cancer in Japan and all over the world.
Integrated genetic and epigenetic analysis identifies colon cancer as three different diseases

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Background: Colon cancer affects 6 percent of the population in the US, and is one of the most common malignances. Colon cancer has been viewed as the result of progressive accumulation of genetic and epigenetic abnormalities. However, this view does not fully reflect the molecular heterogeneity of the disease.

Methods: We have analyzed both genetic (mutations of BRAF, KRAS and p53, as well as microsatellite instability) and epigenetic alterations (DNA methylation of 27 CpG island promoter regions) in a group of 97 primary colorectal cancer patients. Two clustering analyses on the basis of either epigenetic profiling or a combination of genetic and epigenetic profiling were performed to identify subgroups with distinct molecular signatures.

Results: Unsupervised hierarchical clustering of the DNA methylation data identified 3 distinct subgroups of colon cancers named CpG island methylator phenotype (CIMP) 1, CIMP2 and CIMP negative. Genetically, these three clusters correspond to very distinct profiles; CIMP1 cases are characterized by MSI (80%) and BRAF mutations (53%) but rare KRAS and p53 mutations (16% and 11%, respectively). CIMP2 is associated with 92% KRAS mutations but rare MSI, BRAF or p53 mutations (0%, 4% and 31% respectively). CIMP negative cases have a high rate of p53 mutations (71%) and lower rates of MSI (12%) or mutations of BRAF (2%) or KRAS (33%). Clustering based on both genetic and epigenetic parameters also identifies three distinct (and homogeneous) groups that largely overlap with the previous classification. The three groups are independent of age, gender or stage, but CIMP 1 and 2 are more common in proximal tumors.

Conclusion: Integrated genetic and epigenetic analysis reveals that colon cancers correspond to three molecularly distinct diseases. These diseases also differ in terms of histology, precursor lesion and clinical course, suggesting truly distinct pathogenesis.
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DNA methylation as a marker for the past and future

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DNA methylation, a representative epigenetic modification, is stably inherited upon cell replication, and can ‘permanently’ repress gene transcription. In spite of the deep involvement of aberrant methylation in gastric cancers, its induction mechanisms have been unclear.

We quantified methylation levels of eight CpG islands (CGIs) of seven genes in the gastric mucosae of healthy individuals with and without *Helicobacter pylori* (HP) infection, a potent gastric carcinogen. HP infection was detected by the serum antibody test and/or the culture method, reflecting the current or recent infection status. It was found that methylation levels were 5- to 50-fold higher in individuals with current HP infection than those without. We further isolated 48 promoter CGIs that can be methylated in gastric cancers, and found that specific genes were methylated in individuals with HP. It was suggested that a field defect with inactivation of multiple genes was induced by HP infection and that this can be detected by methylation of specific genes.

Methylation levels of the initial eight CGIs were also analyzed in non-cancerous gastric mucosae of cases with a gastric cancer. Individuals with current HP infection showed high methylation levels regardless of the presence or absence of gastric cancers. In contrast, among individuals without current HP infection, cases with a gastric cancer had 2- to 20-fold higher methylation levels than healthy individuals. We further showed that the level of FLNc methylation had an increasing trend in the order of: healthy individuals, cases with a single gastric cancer, and cases with multiple gastric cancers. The risk given by high methylation levels was independent from that given by the extent of endoscopic atrophy. It was indicated that methylation levels in gastric mucosae of individuals without current HP infection can be used to estimate a future risk of gastric cancers.

It is generally known that, for specific cancers, DNA methylation of some genes in cancer tissues is associated with responses to chemotherapies and that of other genes is with patient prognosis. Our study here showed DNA methylation in non-cancerous
tissues is also useful, and might be related to methylation patterns in cancer tissues.

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HER family as potential molecular targets for anticancer therapy against gastrointestinal malignancies

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HER family, a receptor tyrosine kinase including HER1 (EGFR), HER2 (neu/erbB2), HER3 (erbB3) and HER4 (erbB4), regulates essential cellular functions, such as growth, differentiation and apoptosis in epithelial cells, and their activation is associated with carcinogenesis and progression in various cancers including gastrointestinal malignancies. The binding of ligands to the extracellular region of HER family induces receptor homo- or hetero-dimerization and activation of cytoplasmic tyrosine kinase which in turn leads to autophosphorylation and initiation of downstream signaling. Recently, drugs targeting EGFR and HER2 is clinically used for lung and breast cancer patients, and their clinical efficacy has been proved. In gastrointestinal malignancies, a chimeric EGFR monoclonal antibody (mAb) (cetuximab) is approved for clinical application in metastatic colorectal cancer, but molecular targeting therapy for gastric cancer is still unavailable. We found that gastric cancer metastasized to the liver overexpresses HER2 at a significantly higher incidence than primary gastric cancers. We thus developed three new HER2 overexpressing gastric cancer cell lines (GLM-1, GLM-2, GLM-4) without EGFR mutations from such liver metastasis, two of which had HER2 gene amplifications. Interestingly, all these GLM series of cell lines were highly sensitive to gefitinib (Iressa) in vitro, a specific inhibitor of EGFR tyrosine kinase, whereas most of the HER2 low expressing counterparts were not. In these HER2 overexpressing GLM series, Akt, but not ERK1/2 was constitutively phosphorylated, and gefitinib efficiently inhibited this Akt phosphorylation, induced strong apoptosis in vitro and exhibited anti-tumor activity in subcutaneous (sc) tumor xenografts in nude mice. On the other hand, a humanized HER2 mAb (trastuzumab) only weakly inhibited growth of sc tumor xenografts, but showed a marked anti-tumor effect against peritoneal metastasis of HER2 overexpressing GLM-1 cells after intraperitoneal (ip) administration. In these GLM cell lines, no significant inhibition of Akt phosphorylation and induction of apoptosis were observed by trastuzumab treatment in vitro, whereas significant antibody-dependent cell-mediated cytotoxicity (ADCC) was observed by trastuzumab treatment. These results suggest that the anti-tumor effects of gefitinib and the anti-metastatic (peritoneal) effects of trastuzumab against GLM cell lines are mainly due to the effective inhibition of HER2-driven constitutive activation of phosphatidylinositol-3-kinase (PI3K)/Akt pathway and
induction of ADCC, respectively.

In colorectal cancers, we found that intact EGFR expressing COLM-5 cells, a poorly-differentiated colorectal cancer cell line with high metastatic potential established in our laboratory, showed super-sensitivity to both gefitinib and cetuximab in vivo. Primary sc tumor growth, lymph node metastasis and peritoneal metastasis were markedly inhibited by gefitinib and cetuximab monotherapy in some of the treated nude mice cured. However, no apparent apoptosis induction and inhibition of Akt and ERK1/2 phosphorylation were observed in vitro. Although the mechanism of the anti-tumor effect of gefitinib and cetuximab on COLM-5 cells remains unclear, these results suggest the possible presence of a subset of aggressive colorectal cancers with high sensitivity for EGFR targeting drugs. Gastric and colorectal cancers with HER family overexpression would therefore be potential targets for molecular therapy with gefitinib, cetuximab, trastuzumab and possibly other agents.

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Gemcitabine has represented the gold standard for palliative chemotherapy in advanced pancreatic cancer for over a decade. This benchmark was established by a phase III trial which randomized 126 symptomatic patients with advanced pancreatic cancer to either gemcitabine or 5-fluorouracil. Treatment with gemcitabine was associated with improvements in one-year survival (18% versus 2%) and clinical benefit response (24% versus 5%) over 5-FU. Since this trial was published in 1997, many large international phase III trials involving thousands of patients have been conducted comparing gemcitabine alone (as the reference standard) to a gemcitabine combination with either a cytotoxic or molecularly targeted agent. Almost all have failed to meet the standard of improving overall survival.

Gemcitabine and 5-fluorouracil have been the most widely used chemotherapy agents in pancreatic cancer. It is rational, therefore, to combine these agents in the hopes of achieving benefit over either drug alone. SAKK/CECOG compared GemCap, the combination of gemcitabine and capecitabine, an oral prodrug of 5-FU, to gemcitabine alone in patients with locally advanced or metastatic cancer. Consistent with the majority of phase III trials in pancreatic cancer before it, this trial by Herrmann et al. failed to reach their primary endpoint; in this case, a 2-month improvement in median overall survival. ECOG 2297, enrolled 327 patients to standard doses of gemcitabine, given weekly 3 weeks out of 4, with or without 5-FU by bolus infusion at a dose of 600 mg/m2 weekly in the same schedule. The median survival for gemcitabine alone was 5.4 months, compared to 6.7 months with gemcitabine and 5-FU (p=0.09). Modulating the effect of 5-FU, by the use of 24-hour infusion and leucovorin were not successful in improving efficacy when combined with gemcitabine. A phase III trial of 533 patients conducted in the UK comparing GemCap to gemcitabine alone has been reported in abstract form, suggesting a significant survival advantage [HR=0.80] to the combination therapy. Similarly studies of gemcitabine with oxaliplatin, irinotecan and pemetrexed have not shown benefit. After ten years of exhaustive clinical investigations with
gemcitabine doublet regimens in advanced pancreatic cancers, the arguments in favor of combination chemotherapy are modest. The only positive study with gemcitabine-capecitabine is tempered by a similar study that was negative and several other negative gemcitabine-fluoropyrimidine studies.

A wave of new molecularly targeted agents has been emerging into the clinic and many more agents are in preclinical development. The combination of gemcitabine with molecularly targeted agents is a potentially more fruitful avenue of exploration. Encouraging results in phase II trials have been documented with EGFR antagonists, such as erlotinib and cetuximab, as well as antiangiogenic agents, such as bevacizumab. Other agents on the horizon include multitargeted tyrosine kinase inhibitors, such as sorafenib and sunitinib, inhibitors of the mammalian target of rapamycin (mTOR), such as RAD001 and temsirolimus, and Src kinase inhibitors. Gemcitabine and erlotinib, an orally available antagonist of the epidermal growth factor receptor (EGFR), was the first combination regimen to demonstrate statistically significant superiority in terms of overall survival over gemcitabine alone. The hazard ratio was 0.81 which translates to an overall 23% improvement in survival; in absolute terms this translated to an average improvement in survival of 5 weeks. Further analyses suggest there is a subset of patients with pancreatic cancer who receive a greater benefit although at this time we cannot prospectively identify these patients.

Phase II trials of novel agents need to continue and more resources need to be devoted to the development of new agents. These trials also provide the platform for necessary translational research to identify predictive biomarkers for these new agents. By returning to the benchtop from the bedside, we might be able to establish an enriched subset of patients who might benefit from any of a number of available combination therapies. To date, such predictive biomarkers have been elusive for EGFR antagonists and antiangiogenic agents. However, with the use of innovative strategies, such as functional imaging, genomics and other related technologies, we may finally move toward truly individualized and targeted treatment for patients with advanced pancreatic cancer.
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Despite recent advances in imaging modalities, most patients with pancreatic cancer are surgically unresectable at the time of their diagnosis and have an extremely poor prognosis. Even for those who undergo resections, the risk of recurrence is exceedingly high, and patient outcome remains unsatisfactory. Therefore, to improve the prognosis of pancreatic cancer patients, the development of effective non-surgical treatments for this disease is essential.

Gemcitabine, a deoxycytidine analogue, showed a significant impact on survival and clinical benefit response, such as pain alleviation and improved performance status, in a randomized trial comparing it to 5-FU. However, there is still substantial room for improvement in chemotherapy for pancreatic cancer, because gemcitabine can only confer a limited survival benefit. S-1, an oral fluoropyrimidine-based antineoplastic agent consisting of the fluorouracil (5-FU) prodrug tegafur combined with two modulators, gimeracil and potassium oxonate, showed a promising result in our early and late phase II studies. Furthermore, S-1 may be useful in combination with gemcitabine, because the toxicity of S-1 was generally mild and its profile was distinct from that of gemcitabine. Currently, we are conducting a multi-institutional phase II study of this combination treatment for metastatic pancreatic cancer.

A pharmacokinetics study for gemcitabine in Japanese cancer patients showed that carriers of the cytidine deaminase *3 allele had a reduced gemcitabine clearance and a corresponding increase in the neutrophil reduction ratio. Evolving understanding of molecular and genetic biology should facilitate research to establish individualized therapy regimens and to develop novel non-surgical treatment for this disease.
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The future direction of chemotherapy for pancreatic cancer

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Pancreatic cancer is a devastating illness that has the briefest survival of any solid tumor, accounting for approximately 20,000 deaths per year in Japan. The efficacy of gemcitabine was reported by significantly prolonged overall survival demonstrating the existence of a subpopulation of pancreatic cancer patients who benefit from chemotherapy. Prediction of treatment outcome helps tailor more effective treatment strategies and is important to avoid over-treatment. We mention the possibility of tailor made treatment according to the readily available clinical data and molecular processes associated with the development and progression of the disease.

We investigated pre-treatment characteristics and computerized tomography findings in patients, in order to identify the most effective readily available prognostic factors in predicting survival for metastatic pancreatic cancer patients. Multivariate analysis identified performance status, primary tumor location, and C-reactive protein as important independent predictive factors. Patients were divided into three groups according to the score based on coefficients of the Cox model. The internally validated c-index (receiver operating characteristics area under the curve) of this model was 0.711. Applied to another data set, the externally validated c-index was 0.692. This index improved predictive ability in patients with metastatic pancreatic cancer treated with gemcitabine.

We describe the preliminary results of expression of multiple genes in pancreatic cancer with DNA microarray systems. EUS-FNA, which is established as the preferred method to confirm a diagnosis of pancreatic cancer, can also be used to provide pancreatic cancer tissue for microarray analysis. Total mRNA was harvested from each sample which was amplified to provide adequate mRNA for the analysis. The patient with the highest dCMP deaminase or RRM1 resulted in progressive disease (PD) for gemcitabine. DNA microarray-based gene expression profiling combined with EUS-FNA may be a promising tool to predict chemoresistance in advanced pancreatic cancer.

The rapidly evolving understanding of the molecular biology of pancreatic cancer...
may contribute to the development and use of targeted therapies with novel agents for even more effective treatments in the near future.

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Current thoughts on the role of chemotherapy and radiation in advanced head and neck cancer

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The paradigm for the management of advanced squamous cell carcinoma of the upper aerodigestive tract has shifted from a predominantly surgically-based treatment approach to an organ preservation approach that utilizes combinations of chemotherapy and radiation. This approach has been shown to be a valid approach in which organ preservation is feasible and can be attached without sacrificing the potential for meaningful survival. Careful pretreatment clinical, radiographic, and endoscopic assessments of these patients are essential for accurate tumor staging. Treatment strategies focusing on the integration of chemotherapy and radiation will be discussed including the role of induction chemotherapy and tumor response assessment. One of the critical issues is the post-treatment surveillance of these patients. The management of advanced nodal disease in this patient population will be described including the indications and timing of salvage neck dissection. The high incidence of postoperative complications with salvage surgery for local-regional recurrence is mitigated by the use of free tissue transfer. Careful attention should be paid to quality of life and functional outcomes following surgical versus nonsurgical approaches. Targeted treatment using intensity modulated radiation therapy (IMRT) to spare saliva (parotid) function and the pharyngeal constrictors has resulted in improved swallowing results. Our present approach for advanced cancers of the oropharynx is concomitant carboplatin, docetaxel, and IMRT. Our approach for advanced laryngeal cancers not amenable to surgical organ preservation is induction chemotherapy (cisplatin/5-flurouracil) followed by concomitant cisplatin and radiation therapy in responders. Biomarkers such as p53 and Bcl-xL have proven important for predicting response to organ preservation approaches. In oropharynx cancers, presence of human papillomavirus portends an excellent prognosis whereas overexpression of epidermal growth factor receptor portends a poor prognosis. Patients who continue to smoke (“current smokers”) have a poorer outcome than patients who have quit and never smokers.
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Prediction of chemosensitivity for head and neck cancer

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Introduction: Head and neck squamous cell carcinoma (HNSCC) is classified as a tumor with high sensitivity to anti-cancer agents. From the viewpoint of clinical efficacy, however, chemotherapy for head and neck tumors remains challenging. Because conventional clinical and pathologic parameters cannot be used to accurately predict the response to chemotherapy or disease outcome for patients with HNSCC, there exists a great need to identify new markers with which to define the subset of patients who will respond to chemotherapy. To help establish order-made cancer chemotherapy, we performed multigene analysis to identify predictive markers for response to chemotherapy in patients with HNSCC.

Method: Patients undergoing radical treatment for HNSCC at the Department of Head and Neck Surgery, Aichi Cancer Center Hospital were included in the present study, and tumor specimens were collected from surgery or biopsy. 1: The chemosensitivity of surgically respected specimens was investigated in vitro using histoculture drug response assay (HDRA) for 5-fluorouracil (5-FU) and cisplatin, respectively. TS and DPD activities were also measured. 2: Biopsy specimens were taken from patients before administration of induction chemotherapy with 5-FU and cisplatin, and their clinical responses were estimated. 3: Using specimens collected from both surgery and biopsy, we subsequently analyzed the mRNA expression levels of 13 markers that we thought were likely predictors of response to anti-cancer agents. These mRNA expressions were quantified by real-time reverse transcription polymerase chain reaction (real-time RT-PCR) assay, after which we investigated the associations of these mRNA expression levels with chemosensitivity in the HDRA, TS and DPD activities, and clinical response, respectively.

Results: We found that HER2 mRNA expression level was inversely correlated with 5-FU and cisplatin sensitivity in the HDRA, respectively. An inverse correlation was also found between beta-tubulin expression level and cisplatin sensitivity in the HDRA. Moreover, associations of cisplatin sensitivity in the HDRA with MRP1 and Rb1 expression levels were also demonstrated, respectively, albeit just above the level of statistical significance. There was a positive correlation between TS and DPD activity,
and an inverse correlation was detected between TS activity and 5-FU sensitivity in the HDRA. However, associations of TS and DPD activity with their mRNA expression levels were not detected. In the patients who were subjected to induction chemotherapy, the overall response rate was 73.5% (complete response, 38.2%; partial response, 35.3%). However, no significant correlation was observed between any of the investigated mRNA expressions and clinical response to chemotherapy.

Conclusion: Further studies are required to determine whether HER2 expression will be a useful predictive marker for chemosensitivity in patients with HNSCC. A study with additional patients to provide more data on the response to chemotherapy is currently underway.

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Radiotherapy for esophageal cancer -Current status and future directions-

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Carcinoma of the esophagus has been a challenging disease. In contrast to Western countries where the number of patients with adenocarcinoma has been increasing, most patients still have squamous cell carcinoma (SCC) in Japan. Recently, the number of patients with stage I disease has been increasing, although most patients are still diagnosed with advanced disease and dismal prognosis. The standard therapy for patients with resectable disease has been surgery with / without adjuvant therapy in Japan. In 80’s, radiotherapy alone had been indicated in unresectable or medically inoperable patients as a definitive or palliative treatment. In 90’s, chemoradiotherapy (CRT) became a standard for patients who received non-surgical treatment. Recent data suggested that patients who achieved complete response (CR) after CRT had a substantial risk of late toxicity such as pericarditis, pleural effusion, heart failure, and radiation pneumonitis, especially when treated with traditional 2-dimensional radiotherapy. The intergroup randomized study RTOG 9405 / INT 0123, which compared standard dose (50.4 Gy) vs. high dose (64 Gy) radiotherapy with concurrent chemotherapy, also showed that local failure was still dominant even with high dose radiotherapy, and suggested that the tumor control probability of current CRT approaches reached a plateau.

In 2003, we changed the treatment scheme which intended to prevent late toxicity by reducing the dose to normal tissues without compromising the efficacy. This included 3-dimensional conformal radiotherapy, radiotherapy dose reduction from 60 Gy to 50.4 Gy, and selected salvage surgery. So far, the treatment outcome seems good, although it is preliminary and long-term follow up is necessary. We also expect that newer cytotoxic drugs and / or molecular targeted therapy in combination with radiotherapy may improve local control and overall survival in the near future.
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Definitive chemoradiotherapy for stage I-III esophageal squamous cell carcinoma: Current results in Japan.

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**Background:** In Japan, extended radical esophagectomy is thought to be the only way to obtain the cure of EC. **Purpose:** The purpose is to evaluate the efficacy and toxicities of CRT for clinical stage I-III (T1-3N0-1 and M0) esophageal squamous cell carcinoma (ESCC). **Methods:** For stage I, treatment consisted of two 4-week courses of cisplatin 70 mg/m^2^ (day 1) and 5FU 700 mg/m^2^/day (days 1-4) combined with concurrent radiotherapy of 60 Gy in 30 fractions over 7 weeks with one week break. For stage II, III, consisted of two 5-week courses of cisplatin 40 mg/m^2^ (day 1, 8) and 5FU 400 mg/m^2^/day (days 1-5, 8-12) combined with concurrent radiotherapy of 60 Gy in 30 fractions over 8 weeks with 2-week break. For responders, two 4-week courses of chemotherapy of cisplatin 80 mg/m^2^ (day 1) and 5FU 800 mg/m^2^/day (days 1-5) were added. **Results:** From June 1997 to September 2003, consecutive 158 patients were retrospectively analyzed. Patient characteristics were as follows: median age of 63 (range 34-78), male/female: 132/26, PS 0/1/2: 84/70/4, stage I/IIA/IIB/III: 70/25/18/45, scc/others with scc component: 154/4. Of 70 patients (pts) with stage I, there were 64 complete responses (CRs) for CR rate of 91.4% (95% confidence interval (CI); 85-98%). Regarding stage I, 6 pts with residual tumor successfully underwent endoscopic mucosal resection (EMR) or esophagectomy, and local recurrence or new lesion occurred in 11 pts (17%) of 64 CRs, who successfully underwent EMR in 8 and esophagectomy in 3 as salvage treatment, respectively. Of 88 pts with stage II, III, there were 58 CRs for CR rate of 66% (95% CI; 56-75%). Regarding stage II, III, 28 pts (48%) of 58 CRs showed recurrent disease, and 22 pts (79%) of 28 recurrences underwent EMR or esophagectomy as salvage. On the other hand, of 30 non-CRs, there were 10 pts (33%) who underwent EMR or esophagectomy as salvage. With a median follow-up duration of 4.5 years, the 1, 3, 5-year survival rates in pts with stage I were 96%, 79%, and 74%, respectively. With a median follow-up duration of 3.4 years, the 1, 2, 3-year survival rates in pts with stage II, III were 76%, 56%, and 46%, respectively. These survival data are comparable with those obtained by ordinary surgery in Japan. Acute toxicities and
late radiation morbidities increased dependent on the steps of stages, but they were
tolerable and manageable. There was one treatment related death due to severe
diarrhea in stage III EC pt. **Conclusions**: Definitive CRT for stage I-III ESCC is
effective in CR rate and short-term survival with acceptable toxicities, but salvage
treatment for locoregional failure after CRT is necessary to improve the prognosis.

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Systemic chemotherapy for colorectal cancer

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Colorectal cancer is a curative disease. About 50% of patients will be cured by the surgeon, however the other half of patients will experience a relapse. Adjuvant chemotherapy has been established as an important treatment option to increase the cure rate. Twelve cycles of FOLFOX are the most efficacious therapy. Long lasting peripheral neuropathy are however potential sides effects that may not be tolerable for everyone. Oral fluorpyrimidienes either with capecitabine or with UFT are potential less toxic options. Adjuvant therapy is established for node positive disease (UICC stage III), but controversial for stage II patients. A group of high risk stage II patients has been defined; the value of systemic chemotherapy is however less well established.

The liver is the main site of metastases in colorectal cancer. If resectable cure is possible in about 30% - 50% of patients. In patients in which liver metastases have been resected the use of adjuvant chemotherapy is again controversial. Unfortunately, only 15-20% of patients may have respectable disease and treatment of these patients is mostly palliative. Systemic chemotherapy has become more efficacious with the use of regimens including infusional 5-FU modulated with folinic acid and combined with either irinotecan and or oxalipaltin. Response rate of 50-60% may be expected especially in patients with metastases confined to the liver. Phase II studies have been performed with carefully selected patients that were considered non-resectable by their surgeon but probably resectable after systemic chemotherapy. Although criteria of non-resectability may differ between surgeons about 50-70% of these previously non-resectable cases became resectable. In other phase II studies not selecting patients as carefully the resection rate was 20%. Secondary resection of metastases is reported in phase III studies mainly as an incidental event in below 10%. The rate of secondary resection depends on the selection of patients and on the efficacy of the used preoperative chemotherapy. The new targeted agents such as bevacizumab and cetuximab are candidates to further increase the response rate and potential resection rate. Currently available data suggest that cetuximab may be a good candidate as it has single agent efficacy and high response rates have been reported in combination with
chemotherapy. Bevacizumab may cause perioperative bleeding complications and thus has to be used with caution in this setting. Future trials will be necessary to better define the relative value to these new agents.

Secondary resection may be considered as a paradigmatic shift from palliation to cure in patients with metastatic disease and should be considered in any patient with a good response following chemotherapy.

Nowadays, we have to decide whether a curative approach might be possible in order to initiate the most efficacious regimen that may result in resection of metastases. Hereby, a higher degree of toxicity may be acceptable to achieve this goal. In a more palliative approach, a low degree of toxicity with a maximum effect of tumor control is the aim and the sequential use of chemotherapy agents probably with a stop and go strategy to maximise quality of life in patients is a potential strategy.

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Chemotherapy for colorectal cancer is a rapidly evolving field. This is largely due to the development of various novel agents, such as irinotecan, oxaliplatin, capecitabine, bevacizumab, cetuximab, and panitumumab, over the past decade. These agents have provided not only survival prolongation in patients with metastatic disease but also additional cure rate after curative resection in stage III disease. Although the approval status of these agents had been far behind from the Western countries, the delay is now being improved and these advantage will be available very soon for the Japanese patients.

There are few ethnic differences in PK / PD of these new agents between the West and Japanese population, except for oral fluorouracils where Japanese patients have lower incidence of diarrhea as compared to Caucasians. Nowadays, oxaliplatin or irinotecan in combination with infusional fluorouracil (FOLFOX / FOLFIRI) are becoming popular in most of the Japanese institutions where medical oncologists lead the chemotherapy. The registration trials of molecular targeting agents such as bevacizumab, cetuximab, and panitumumab have already completed and these agents will be commercially available soon. During these developments, there have been no obvious differences in safety and efficacy results as compared with those in overseas and we are ready to accept global results. According to the recent change of regulatory guidelines in Japan which facilitate to enter into global studies, we are also planning to participate global IND studies with newly developing (next generation) agent. In case of adjuvant trials, several Japanese institutions have participated in a global IND trial comparing FOLFOX4 with FOLFOX4 + bevacizumab or XELOX + bevacizumab (AVANT study). The number of post-marketing studies is also increasing and various combination regimens including oral fluorouracil which seems favorite for Japanese population, and some of them are being investigated in randomized trials. These studies, either global or domestic, will resolve the issues whether there are true ethnic differences in terms of efficacy and safety between Japanese and non-Japanese
Mortality rate from colorectal cancer in Japan has already become similar to those in the West and it should be an urgent issue for Japanese health. We have just entered into the global development line of new agents for colorectal cancer and will play an important role in this field, which would provide more advantage for the patients with colorectal cancer over the world.

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**Hepatic arterial infusion chemotherapy for liver metastasis from colorectal cancer**

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Some RCTs comparing 5-FU based systemic chemotherapy and hepatic arterial infusion chemotherapy (HAIC) have not shown the impact of HAIC contributes to improving on the survival prolongation in patients with liver metastasis from colorectal cancer in the last 20 years. In these studies, although HAIC was superior to systemic chemotherapy on the local response, HAIC had low feasibility and high incidence of extra-hepatic foci.

However, there is a great difference in techniques for HAIC between western countries and Japan. The indwelling catheter for HAIC is placed under laparotomy in western countries, while it is performed with percutaneous radiological procedures in Japan. HAIC in Japan actually has high feasibility and low invasion. In Japanese phase II studies, the median survival time (MST) of HAIC with 5-FU only showed over 20 months. At that time, there were not new agents such as irinotecan and oxaliplatin. But since HAIC was the regional therapy, it could not prevent the extra-hepatic disease from spreading anyway.

Now systemic chemotherapy for advanced or recurrent colorectal cancer has approximately 50% of the response rate and over 20 months of the MST, but liver metastasis is still one of the most important survival limiting factors. In US, combination therapy with hepatic arterial infusion and systemic irinotecan or oxaliplatin might be more useful recently. HAIC may have a potential role in pushing up the MST of patients with liver metastasis even after the failure of systemic chemotherapy.

HAIC supported by the adequate techniques is safely administered. HAIC with 5-FU only is reasonable, while new agents are costly. In considering the disease condition as well as quality of life and medical expenses of patients, we are groping the new strategy in which HAIC is performed only in the time when liver metastasis is dominant and it is converted into systemic chemotherapy in the time when extra-hepatic lesions are growing.
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