2009년 제9차
한국임상암학회 학술대회

The 9th Annual Meeting of Korean Association for Clinical Oncology

- 일 시: 2009년 11월 21일(토) 08:30~17:45
- 장 소: 신촌세브란스병원 본관 은영대강당 및 세미나실
# The 9th Annual Meeting of Korean Association for Clinical Oncology

- **November 21, 2009 (SAT.)**

## Programme

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<td>17:30-17:45</td>
<td>우수 발표 시상 및 폐회</td>
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일시: 2009년 11월 21일(토) 08:30 ~ 17:45
장소: 신촌세브란스병원 본관 은행택당 및 세미나실

08:30~08:50 이어  한국암학회 회장 이상재
08:50~09:00 Opening Remark

09:00~11:00 Oral Presentation (No. O-01~12)
Session 1. Breast Cancer (No. O-1~3) Chairpersons 임영혁(성균관의대), 서재홍(고려의대)
Session 2. Breast Cancer (No. O-4~6) Chairpersons 김성배(울산의대), 김지현(서울의대)
Session 3. Gastric Cancer (No. O-7~9) Chairpersons 김태유(서울의대), 권혁찬(동아의대)
Session 4. Gastric Cancer, Hepato-Biliary-Pancreatic Cancer (No. O-10~12)

11:00~11:15 Coffee Break

11:15~12:00 Plenary Lecture I Chairperson: 박근철(성균관의대)
Best Strategy for Personalizing Treatment in Advanced & Metastatic NSCLC
Dr. Mark Vincent (University of Western Ontario, Canada)

12:00~13:10 Lunch

13:10~13:55 Plenary Lecture II Chairperson: 노정실(국립암센터)
Progress in Oncology; PARP Inhibition
John E. Pippen Jr. M.D., FACP (Baylor-Sammons Cancer Center, USA)

13:55~14:15 무의미한 연명치료의 중단 허대석(서울의대)
14:15~14:35 연명치료 중단 대법원 판결의 의의와 과제 박형욱(연세의대)
14:35~14:55 연명치료 중지 지침과 밀기 임 환자 관리에 관한 윤리적 고찰 김장헌(울산의대)
14:55∼15:15  Panel Discussion
15:15∼15:30  Coffee Break

15:30∼16:30  Oral Presentation (No. O-13∼24)

<은명대강당>
Session 5. Lung Cancer (No. O-13∼15)  Chairpersons  김상위(울산의대),  김동완(서울의대)

<세미나실>
Session 7. Colorectal Cancer (No. O-19∼21) Chairpersons  신동복(가천의대),  김종광(경북의대)
Session 8. Others (No. O-22∼24)  Chairpersons  신상원(고려의대),  김도연(동국의대)

16:30∼17:30  Poster Discussion

1. Breast Cancer (No. P-1∼3)  Discussant  이근석(국립암센터)
2. Gastric Cancer (No. P-11∼14)  Discussant  라선영(연세의대)
3. Colorectal Cancer (No. P-22∼25)  Discussant  신상준(연세의대)
4. Lung Cancer (No. P-30)  Discussant  이대호(울산의대)

17:30∼17:45  우수 Presentation 시상 및 패퇴
Session 1. Breast Cancer

Chairpersons: 임영혁(성균관의대), 서재홍(고려의대)

Do-Youm Oh (Seoul National University)

O-02 Who Can Have Benefit from Intensified Surveillance Program in Postoperative Breast Cancer Patients?
Soohyeon Lee (Sungkyunkwan University)

O-03 Clinical Features and Course of Brain Metastases in Triple Negative Breast Cancer: Comparison with HER2+ and Other Type
Geundoo Jang (University of Ulsan)

Session 2. Breast Cancer

Chairpersons: 김성배(동아의대), 김지현(서울의대)

O-04 The Prognostic Factors for the Recurrent Breast Cancer Patients with Isolated, Limited Number of Lung Metastases and the Implication of Pulmonary Metastasectomy
Ho-Young Yhim (Seoul National University)

O-05 The Clinical Outcome of Chemotherapy Induced Amenorrhea in Premenopausal Young Breast Cancer Patients with Long Term Follow Up
Minkyu Jung (Yonsei University)

O-06 Comparable Efficacies between Premenopausal and Postmenopausal Metastatic Breast Cancer Patients by Letrozole with and without Goserelin as First Line Hormone Therapy: A Phase II Parallel Group Study
In Hae Park (National Cancer Center)

Session 3. Gastric Cancer

Chairpersons: 김태윤(동아의대), 권혁찬(동아의대)

O-07 DOS (Docetaxel, Oxaliplatin and S-1) Combination Chemotherapy in Metastatic Gastric Cancer: Results of a Phase II Study
Boram Han (Hallym University)

O-08 Bone Morphogenetic Protein-2 (BMP-2) Levels Are Elevated in Patients with Gastric Cancer and Correlate with Disease Progression
Yong Park (Korea University)

O-09 Stage IV(M0) as a Separate Prognostic Subgroup in Patients with Gastric Adenocarcinoma
Ki Hwan Kim (Seoul National University)
**Session 4. Gastric Cancer, Hepato-Biliary-Pancreatic Cancer 10:30 ~ 11:00, 은평대강당**

**Chairpersons:** 김영홍(고려의대), 장홍문(울산의대)

**O-10** The Incidence, Risk Factors and Prognostic Implications of Venous Thromboembolism in Patients with Gastric Cancer
Keun-Wook Lee (Seoul National University)

**O-11** Outcomes of Multiple Salvage Chemotherapy in Advanced Gastric Cancer: Implications for Clinical Practice and Trial Design
Yong Wha Moon (Yonsei University)

**O-12** Phase II Study of Fixed Dose-rate Infusion of Gemcitabine and UFT Combination Chemotherapy in Patients with Advanced Bile Duct Cancer: Daegu Gyeongbuk Oncology Group
Sung Hwa Bae (Catholic University of Daegu)

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**Session 5. Lung Cancer 15:30 ~ 16:00, 은평대강당**

**Chairpersons:** 김상휘(울산의대), 김동환(서울의대)

**O-13** Selection of Patients Who Could Most Benefit from Maintenance Therapy in Non-small Cell Lung Cancer
Jong-Mu Sun (Sungkyunkwan University)

**O-14** Pretreatment FDG-PET Can Predict Survival Rates Following Definitive Radiotherapy in Lymph Node Positive Non-small Cell Lung Cancer Patients
Hyun-Cheol Kang (Seoul National University)

**O-15** Impact of Environmental Tobacco Smoke on the Incidence of Mutations in Epidermal Growth Factor Receptor Gene in Never Smoker Patients with Non-small Cell Lung Cancer
Young Joo Lee (National Cancer Center)

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**Session 6. Lung Cancer, Head & Neck Cancer 16:00 ~ 16:30, 은평대강당**

**Chairpersons:** 이종석(서울의대), 윤환중(충남의대)

**O-16** Distinct Clinico-pathologic Characteristics of Non-small Cell Lung Cancer Patients with ALK Rearrangement: EGFR Mutations and ALK Rearrangement Are Not Mutually Exclusive
Youngil Koh (Seoul National University)

**O-17** Docetaxel Plus Carboplatin Versus Docetaxel for the Patients with Old Age or Poor Performance in Advanced Non-small Cell Lung Cancer: Randomized Phase III Study
Eun Kyoung Kim (University of Ulsan)

**O-18** The Efficacy of \(^{18}\)FDG-PET Scan One-month after Definitive Radiotherapy in Nasopharyngeal Carcinoma
O Kyu Noh (University of Ulsan)
Session 7. Colorectal Cancer

Chairpersons: 신동복(가천의대), 김종광(경북의대)

O-19  Tailored-Dose Capecitabine Chemotherapy as Adjuvant Treatment in Elderly Colon Cancer Patients  
Hye Jung Chang (Seoul National University)

O-20  Clinical Impact of Microsatellite Instability in Colon Cancer following Adjuvant FOLFOX Therapy  
Seung Tae Kim (Sungkyunkwan University)

O-21  Significance of Cyclooxygenase-2 in Predicting Clinical Outcome of Locally Advanced Rectal Cancer Patients Treated with Postoperative Adjuvant Chemoradiation  
Jun Won Kim (Yonsei University)

Session 8. Others

Chairpersons: 신상원(고려의대), 김도연(동국의대)

O-22  High Number of Tumor-infiltrating FOXP3-Positive Regulatory T-cells Are Associated with Improved Clinical Outcomes after Chemotherapy in Patients with Ocular Adnexal MALT Lymphoma  
Ki Hwan Kim (Seoul National University)

O-23  Cancer Pain Management with Hydromorphone OROS in Korean Cancer Patient: Evaluation of Its Clinical Usefulness in Reduction of Breakthrough Pain Medication Frequency: Multicenter, Prospective, Open-label Study  
Kyung Hee Lee (Yeungnam University)

O-24  A Cross-Sectional Study of Imatinib Plasma Trough Levels in Patients with Advanced Gastrointestinal Stromal Tumors: Impact of Gastrointestinal Resection on Exposure to Imatinib  
Changhoon Yoo (University of Ulsan)

【Poster Discussion】

Session 1. Breast Cancer

Discussant: 이근석(국립암센터)

P-01*  MDR1/ABCB1 Single Nucleotide Polymorphism (SNP) in Stage II/III Breast Cancer Patients Who Received Docetaxel and Doxorubicin Neoadjuvant Chemotherapy  
Hee-Jun Kim (Seoul National University)

P-02*  Predictive Factors for Pathological Complete Response (pCR) after Preoperative Chemotherapy in 338 Patients with Stage II, III Breast Cancer  
Jaechon Jeong (National Cancer Center)

P-03*  An Observational Study of Docetaxel-Based Adjuvant Chemotherapy in Breast Cancer Patients at High Risk of Recurrence In Asia-Pacific  
Sung-Bae Kim (University of Ulsan)
Session 2. Gastric Cancer

P-11* Predictive Value of Orotate Phosphoribosyltransferase Expression for Treatment Outcomes in Patients with Advanced Gastric Cancer Treated with 3-weekly S-1 Plus Cisplatin Chemotherapy
Keun-Wook Lee (Seoul National University)

P-12* Enhancer of Zeste Homolog 2 Expression Is Associated with Tumor Cell Proliferation and Metastasis in Gastric Cancer
Jung-Hye Choi (Hanyang University)

P-13* Expression of Bax Predicts Outcome in Advanced Gastric Cancer Patients Treated with 5-Fluorouracil, Leucovorin, and Oxaliplatin Palliative Chemotherapy
Seong Hyun Jeong (Ajou University)

P-14* High SUV in FDG PET/CT Predicts Worse Prognosis in Metastatic Gastric Cancer Patients Receiving Palliative Chemotherapy
Yo-Han Cho (Konkuk University)

Session 3. Colorectal Cancer

P-22* RIPK1 Gene Polymorphism as a Prognostic Marker for Survival in Patients with Colorectal Cancer
Yee Soo Chae (Kyungpook National University)

P-23* Prognostic Impact of MicroRNA-related Gene Polymorphisms on Survival of Patients with Colorectal Cancer
Shi Nae Kim (National Cancer Center)

P-24* Randomized Phase III Trial Comparing Preoperative versus Postoperative Radiotherapy with Capecitabine in Locally Advanced Rectal Cancer
Jin-hong Park (University of Ulsan)

P-25* A Pilot Study of Neoadjuvant Chemoradiation with Higher Dose Enteric-coated Tegafur/Uracil Plus Leucovorin for Locally Advanced Rectal Cancer
Sun Young Kim (National Cancer Center)

Session 4. Lung Cancer

P-30* Comparison of Survival Difference according to T Stage between the Current (6th) and the Proposed (7th) TNM Staging System in Non-Small Cell Lung Cancer (a Single Center Experience)
Byeong Seok Sohn (University of Ulsan)
P-01* MDR1/ABCB1 Single Nucleotide Polymorphism (SNP) in Stage II/III Breast Cancer Patients Who Received Docetaxel and Doxorubicin Neoadjuvant Chemotherapy
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Sung-Bae Kim (University of Ulsan)

P-04 Global Breast Cancer Trends and Challenges: A South Korean Perspective
Sung-Bae Kim (University of Ulsan)

P-05 Skin and Soft Tissue Infiltration Patterns of Breast Cancer according to Subtypes at the Time of Skin Metastases
Jeehyun Kong (Sungkyunkwan University)

P-06 Heterogeneity of Triple Negative Breast Cancer (TNBC): TNBC Might be Divided into Two or More Subgroups by Clinicopathologic Findings
Jung A Kim (Sungkyunkwan University)

P-07 Trastuzumab Mediated Cardiac Dysfunction Outside Clinical Trials: A Single Center Experience in Asia
Jin Hyun Park (Seoul National University)

P-08 Phase II Study of Irinotecan Plus Capecitabine in Patients with Anthracycline and Taxane Pretreated Metastatic Breast Cancer
Keun Seok Lee (National Cancer Center)

P-09 Single Nucleotide Polymorphisms of CYP19A1, rs10459592 and rs4775936 Predict Clinical Benefit of Letrozole in Patients with Metastatic Breast Cancer
In Hae Park (National Cancer Center)

P-10 Predictors of 4 or More Positive Axillary Nodes in Patients with Node-positive T1-2 Breast Carcinoma: The Indications for Adjuvant Irradiation of the Level III Axilla and Supraclavicular Fossa
Jong Hoon Lee (The Catholic University of Korea)

P-11* Predictive Value of Orotate Phosphoribosyltransferase Expression for Treatment Outcomes in Patients with Advanced Gastric Cancer Treated with 3-weekly S-1 Plus Cisplatin Chemotherapy
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High SUV in FDG PET/CT Predicts Worse Prognosis in Metastatic Gastric Cancer Patients Receiving Palliative Chemotherapy
Yo-Han Cho (Konkuk University)

**P-15**
A Retrospective Analysis of Stage IB Gastric Cancer (GC) Patients Who Had Underwent D2 Gastrectomy with or without Adjuvant Chemoradiotherapy
Jung-Hoon Kim (Sungkyunkwan University)

**P-16**
Oxaliplatin Combined with Continuous Infusion of 5-fluorouracil as First-line Chemotherapy in Patients with Metastatic or Recurrent Gastric Adenocarcinoma
Kyung Jin Oh (Yonsei University)

**P-17**
Clinical Outcomes and Prognostic Factors of Metastatic Gastric Carcinoma Patients Who Experience Gastrointestinal Perforation
Myoung Hee Kang (National Cancer Center)

**P-18**
Clinical Outcome of Advanced Gastric Cancer Patients with Bone Marrow Metastases
Ji-Yeon Kwon (Soonchunhanyang University)

**P-19**
Oxaliplatin, 5-FU, Folinic Acid as First-line Treatment in Metastatic or Recurrent Gastric Cancer
Han-Jo Kim (Soonchunhanyang University)

**P-20**
A Phase II Study of Biweekly Chemotherapy with Irinotecan, 5-fluorouracil, and Leucovorin (FOLFIRI) in Patients with Advanced Gastric Cancer after Failure of Prior Chemotherapy Including Taxane, Fluoropyrimidine, Platinum
Myoung Joo Kang (University of Ulsan)

**P-21**
A Phase II Study of Docetaxel and Oxaliplatin Combination as First-line Chemotherapy in Recurrent Gastric Cancer Patients after Fluoropyrimidine and/or Cisplatin Adjuvant Treatment
Yoon Hee Choi (Korea Cancer Center Hospital)

**P-22**
RIPK1 Gene Polymorphism as a Prognostic Marker for Survival in Patients with Colorectal Cancer
Yee Soo Chae (Kyungpook National University)

**P-23**
Prognostic Impact of MicroRNA-related Gene Polymorphisms on Survival of Patients with Colorectal Cancer
Shi Nae Kim (National Cancer Center)

**P-24**
Randomized Phase III Trial Comparing Preoperative versus Postoperative Radiotherapy with Capecitabine in Locally Advanced Rectal Cancer
Jin-hong Park (University of Ulsan)

**P-25**
A Pilot Study of Neoadjuvant Chemoradiation with Higher Dose Enteric-coated Tegafur/Uracil Plus Leucovorin for Locally Advanced Rectal Cancer
Sun Young Kim (National Cancer Center)

**P-26**
Phase II Study of Biweekly S-1 and Oxaliplatin Combination Chemotherapy in Metastatic Colorectal Cancer
Junsik Hong (Seoul National University)

**P-27**
Brain Metastases from Colorectal Carcinoma: Prognostic Factors and Outcome
Minkyu Jung (Yonsei University)
P-28 Mitomycin-C, 5-fluororacil and Leucovorin as a Salvage Therapy in Patients with Metastatic Colorectal Adenocarcinoma: A Retrospective Analysis
Eun Joo Kang (Korea University)

P-29 The Effect of DNA Mismatch Repair (MMR) Status on Oxaliplatin-based First-line Chemotherapy as in Recurrent or Metastatic Colon Cancer
Seung Tae Kim (Sungkyunkwan University)

P-30* Comparison of Survival Difference according to T Stage between the Current (6th) and the Proposed (7th) TNM Staging System in Non-Small Cell Lung Cancer (a Single Center Experience)
Byeong Seok Sohn (University of Ulsan)

P-31 Results of Conventional Definitive 3D-CRT alone for Non-small Cell Lung Cancer
Yu Sun Lee (University of Ulsan)

P-32 An Association of the Age at Diagnosis with the Presence of EGFR Mutations in Female Patients with NSCLC: A Single-Institution Retrospective Analysis
Yoon Hee Choi (Korea Cancer Center Hospital)

P-33 A Phase II Study of Combination Chemotherapy with Docetaxel and Carboplatin for Elderly Patients with Advanced Non-small Cell Lung Cancer
Hye Jin Kim (Seoul Veterans Hospital)

P-34 Elevated Serum C-reactive Protein as a Prognostic Marker in Small Cell Lung Cancer
Soojung Hong (Yonsei University)

Youngil Koh (Seoul National University)

P-36 Randomized Phase II Trial of Pemetrexed versus Gefitinib in Previously Treated Non-small Cell Lung Cancer; Preliminary Results
Eun Kyung Cho (Gachon University)

P-37 Irinotecan Plus Carboplatin in Patients with Extensive-disease Small Cell Lung Cancer
Eun Kyung Cho (Gachon University)

P-38 Interstitial Pneumonitis after Treatment with Pemetrexed for Non-small Cell Lung Cancer
Kyung-Hyun Kim (Kangwon National University)

P-39 Asymptomatic Pulmonary Embolism in Lung Cancer Patients: The Impact on Survival and the Significance of Anticoagulation Therapy
Jong-Mu Sun (Sungkyunkwan University)

P-40 Phase II Study of a Biweekly Schedule of Docetaxel and Cisplatin in Patients with Metastatic Non-small Cell Lung Cancer
Gyeong-Won Lee (Gyeongsang National University)

P-41 Comparison of Erlotinib (Tarceva™) versus Gefitinib (Iressa®) as the Second Line Therapy for the Treatment of Advanced Non-Small Cell Lung Cancer Patients: A Randomized Phase II Trial
Ji Eun Uhm (Sungkyunkwan University)
P-42 The Overexpression of Ribonucleotide Reductase Regulatory Subunit M1 (RRM1) Protein Is a Predictor of Shorter Survival to Gemcitabine-based Chemotherapy in Advanced Non-small Cell Lung Cancer (NSCLC)
Jae Jin Lee (Kyung Hee University)

P-43 Second Line Chemotherapy with S-1 for Head and Neck Cancer
Bo Ran Kwon (Pusan National University)

P-44 The Metabolic Tumor Volume Predicts for Response to Treatment and Progression Free Survival in Head and Neck Cancer
Young Mi Seol (Pusan National University)

P-45 A Phase II Study of Combination Chemotherapy with Capecitabine and Cisplatin in Patients with Metastatic or Recurrent Head and Neck Cancer
Young-Woong Won (Sangkyunkwan University)

P-46 Immunohistochemical Study to Identify Biomolecular Markers for Prediction of Outcomes of Radiotherapy for Nasopharyngeal Carcinoma
Yeon-Joo Kim (Seoul National University)

P-47 Intensity-modulated Radiotherapy for Carcinoma of Oropharynx and Oral Cavity: Treatment Outcome and Complication
Jihye Cha (Yonsei University)

P-48 Comparison of Clinical Features and Treatment Outcome in Elderly Head and Neck Cancer Patients with Younger Patients
Gak-Won Yun (Chonnam National University)

P-49 Update of a Phase II Trial of Induction Chemotherapy with Docetaxel/Capecitabine (DC) for Patients with Locally Advanced Head and Neck Cancer
Young-Joon Yang (Changnam National University)

P-50 Phase II Study of Docetaxel, Cisplatin and 5-FU Induction Chemotherapy Followed by Chemoradiotherapy in Advanced Nasopharyngeal Cancer
Woo Kyun Bae (Chonnam National University)

P-51 A Phase II Study of Gemcitabine, 5-FU and Cisplatin Combination Chemotherapy for Patients with Advanced Biliary Tract Cancer
Hye Young Lee (Inje University)

P-52 Stereotactic Body Radiotherapy for the Patients with Primary Unresectable Hepatocellular Carcinoma: Dosimetric Parameters Predicting the Hepatic Complication
Seok Hyun Son (The Catholic University of Korea)

P-53 Sorafenib for Recurrent Hepatocellular Carcinoma after Liver Transplantation
Dok Hyun Yoon (University of Ulsan)

P-54 The Significance of ICG R15 in Predicting Radiation-induced Hepatic Toxicity for Radiotherapy of Hepatocellular Carcinoma Patients
Hong In Yoon (Yonsei University)

P-55 Clinical and Prognostic Features of Solitary Plasmacytoma: Outcome Analysis of 29 Cases in SNUH
Hyeon Kang Koh (Seoul National University)

P-56 Efficacy of CODOX-M/IVAC in Patients with Adult Burkitt’s Lymphoma (BL)
Hyun Jung Lee (Seoul National University)
P-57 Efficacy of L-asparaginase-based Chemotherapy in Patients with Extranodal NK/T Cell Lymphoma
Jeong-Ok Lee (Seoul National University)

P-58 A Case of Monoclonal Gammapathy in Extranodal Marginal Zone B-cell Lymphoma (ENMZL)
Do Yeun Kim (Dongguk University)

P-59 Is Inactivation of O6-methylguanine DNA Methyltransferase Still a Favorable Prognostic Factor of Patients with Diffuse Large B-cell Lymphoma in the Era of R-CHOP Chemotherapy?
Gyeong-Won Lee (Gyeongsang National University)

P-60 Salvage Therapy with Gemcitabine, Ifosfamide, Dexamethasone, and Oxaliplatin (GIDOX) for B-Cell Non-Hodgkin’s Lymphoma
Byeong-Bae Park (Hanyang University)

P-61 Concurrent Chemoradiotherapy with Weekly Docetaxel and Cisplatin in Advanced Esophageal Cancer
Hyun-Jeong Shim (Chonnam National University)

P-62 The Safety and Effectiveness of Central Venous Catheterization in Patients with Cancer: A Prospective Observational Study
Hyun Jung Kim (Soonchunhyang University)

P-63 Hypofractionated Intensity-Modulated Radiotherapy using Simultaneous Integrated Boost Technique with Concurrent and Adjuvant Temozolomide for Glioblastoma
Eunjin Jwa (University of Ulsan)

P-64 2006 Cancer Pain Survey in Daegu-Gyeongbuk Area
Jin Young Kim (Keimyung University)

P-65 Primary Mediastinal Germ Cell Tumors with Hematologic Disorders: A Case Report and Review of the Literature
Jin Ho Choi (Seoul National University)

P-66 Concurrent Chemoradiotherapy Compared with Radiotherapy Alone in Intermediate-Risk Stage IB-IIA Cervical Cancer After Hysterectomy and Pelvic Lymphadenectomy
Chang Hoon Song (Seoul National University)

P-67 Adenocarcinoma of the Uterine Cervix-analysis of Treatment Outcome and Prognostic Factors
Young Suk Kim (Yonsei University)

P-68 Experience on Chemotherapy Related Neutropenic Fever Seen at Emergency Room of Inha University Hospital
Joo Han Lim (Inha University)

P-69 Pathophysiological Role of Hormones and Cytokines in Cancer Cachexia
Hyun Jung Kim (Soonchunhyang University)

P-70 Sunitinib for Unselected Korean Patients with Advanced Renal Cell Carcinoma: A Comparable Efficacy with Different Toxicity Profiles
Hyo Song Kim (Yonsei University)
P-71 Interval between Diagnosis of Advanced Cancer and Cessation of Active Anti-cancer Treatment Can Predict Survival in Terminally Ill Cancer Patients Yu Jung Kim (Seoul National University)

P-72 Employment Status and Work-Related Difficulties among Family Members of Terminally Ill Patients Compared with the General Population Seon Young Kim (National Cancer Center)

P-73 Ondansetron Induced Extrapyramidal Reactions Ha-Yeon Lee (Chung-Ang University)
The 9th Annual Meeting of
Korean Association for Clinical Oncology

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Plenary Lecture I

좌장: 박근철(성균관의대)
Best Strategy for Personalizing Treatment in Advanced and Metastatic NSCLC

M. Vincent, MB ChB, FRCP, MRCP (UK)
University of Western Ontario, Canada

TOPIC ONE

WHAT IS “PERSONALIZED TREATMENT”?

CONNOTATIONS OF “PERSONALIZED TREATMENT”
THE TWELVE CONCEPTS OF “PERSONALIZED TREATMENT”

1. **Discrimination** amongst competing alternative treatments.

2. **Modularity**, acknowledging the existence of components which can be purposefully employed or omitted.

3. **Creativity**, at least admitting the possibility of novelty in drug combinations, sequencing and dosing.

4. **Tailoring**, implying the construction of an appropriate plan, reflecting the totality of factors influencing the selection.

5. **Definitive**, necessarily attaining superior efficacy.

6. **Rationality**, using drugs directed against targets defining and/or driving the cancer.

---

THE TWELVE CONCEPTS OF “PERSONALIZED TREATMENT”

7. **Empiricism**, not discarding traditional, “untargeted” drugs if well supported by data.

8. **Tolerability**, accommodates patient idiosyncrasies in pharmacogenomics and other parameters influencing toxicity.

9. **Sympathy**, i.e., reflects the patient’s priorities and limits.

10. **Balance**, reflecting the trade-offs which informed patients often have to make.

11. **Adaptable**, responsive to changing circumstances and unexpected events.

12. **Sophistication**, exploiting a complex system of knowledge.

---

**TOPIC TWO**

**PERSONALIZED TREATMENT: THE IDEAL**
**PERSONALIZED TREATMENT: THE IDEAL**

**INPUTS**
- Therapeutic armamentarium
- Tumour biopsy
- Pharmacogenomics
- Non-genomic patient parameters
- Patient priorities & preferences

**“BLACK BOX”**

**INTEGRATION + ANALYSIS:**
- Predictions of efficacy/toxicity
- Best options/alternatives
- Accommodation for patient wishes

**OUTPUT**
- Flexible plan for serial treatments
  - Best option now
  - Preemptive plan for toxicity avoidance
  - Scheduled monitoring

---

**TOPIC THREE**

**STATE OF TRANSITION**

---

**THE PAST**
- Acute, fulminating illness
- Limited therapeutic options
- Little mechanistic insight
- MST 4-6 m
- Harsh, toxic treatments
- Rapid downhill course
- Untargeted treatments
- “One size fits all”

**THE FUTURE**
- Chronic disease model
- Many therapeutic options
- Extensive mechanistic insight
- MST >2 yrs
- Gentle, tolerable treatments
- Long periods of stability/remission
- Highly targeted treatments
- Extensive tailoring
The 9th Annual Meeting of Korean Association for Clinical Oncology

**BIOMARKERS**

- NO
- YES

**MAINTENANCE**

- NO
- YES

<table>
<thead>
<tr>
<th>CURRENT</th>
<th>TRANSITIONAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRANSITIONAL</td>
<td>IMMINENT STD-OF-CARE</td>
</tr>
</tbody>
</table>

**TOPIC FOUR**

**THE CONCEPT OF THE DIAGNOSTIC BUCKET**

![Whole genome path array CGH](image)

*Figure 1: Comparison of copy AC and SC/C genomes. Proportion of alteration were separately determined for AC and SC/C samples and visualized using CytoGen software version 2.7.1, as described in Figure 1. The plot was then overlaid to illustrate value of differences between the 2 populations: Yellow represents regions frequently altered in both AC and SC/C, while red and green regions are more frequently altered in AC or SC/C, respectively.*

*Garus C et al. Int J Cancer, 2006*
Table 1. History of Lung Adenocarcinoma Subclassification According to the WHO

<table>
<thead>
<tr>
<th>WHO Classification (2009)</th>
<th>Invasive ADC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solid adenocarcinoma</td>
<td>Acinar pattern predominant</td>
</tr>
<tr>
<td>Acinar adenocarcinoma</td>
<td>Solid pattern predominant</td>
</tr>
<tr>
<td>Adenocarcinoma, mixed subtype</td>
<td>Papillary pattern predominant</td>
</tr>
<tr>
<td>Adenocarcinoma, mixed adenocarcinoma</td>
<td>Micropapillary pattern, predominant</td>
</tr>
<tr>
<td>Adenocarcinoma, mixed mucinous adenocarcinoma</td>
<td>Solid pattern predominant</td>
</tr>
<tr>
<td>Adenocarcinoma, mixed variant adenocarcinoma</td>
<td>Solid pattern predominant</td>
</tr>
<tr>
<td>Adenocarcinoma, mixed mucinous adenocarcinoma</td>
<td>Solid pattern predominant</td>
</tr>
<tr>
<td>Adenocarcinoma, mixed papillary adenocarcinoma</td>
<td>Solid pattern predominant</td>
</tr>
<tr>
<td>Adenocarcinoma, mixed micropapillary adenocarcinoma</td>
<td>Solid pattern predominant</td>
</tr>
<tr>
<td>Adenocarcinoma, mixed solid adenocarcinoma</td>
<td>Solid pattern predominant</td>
</tr>
<tr>
<td>Adenocarcinoma, mixed acinar adenocarcinoma</td>
<td>Solid pattern predominant</td>
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<tr>
<td>Adenocarcinoma, mixed papillary adenocarcinoma</td>
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<td>Adenocarcinoma, mixed solid adenocarcinoma</td>
<td>Solid pattern predominant</td>
</tr>
</tbody>
</table>
| Adenocar
... Or Not Enough?

“Things should be made as simple as possible but not any simpler”

Albert Einstein (1879-1955)

The Concept of the Diagnostic Bucket

Diagnostic Information
(Tumour, Histology/BioMarkers + Patient Demographics/Clinical)
- Supportive
- Decisive (“Disambiguator”)

etc. ———— etc.

IDIOSYNCRATIC PATIENT INFORMATION
REAL-WORLD LIMITATIONS

"Personalized" Treatment

Level of the subgroup

Level of the individual patient

PERSONALIZED MEDICINE TODAY

Subgroup Ascertainment + Individual Patient Data
+ Rule of Therapy + Therapeutic options
= Personalized Treatment
# Topic Five

The Eight(?) Diagnostic Buckets of Lung Cancer

<table>
<thead>
<tr>
<th>The Eight Buckets of Lung Cancer</th>
<th>Required</th>
<th>Supportive</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>EGFR mt+ve</td>
<td>Adenocarcinoma kras TTF1+EGFR FISH+</td>
</tr>
<tr>
<td>II</td>
<td>Neverlight ex-smoker EGFR wt Adenocarcinoma</td>
<td>Absence of classical kras mutation</td>
</tr>
<tr>
<td>III</td>
<td>(Ex)smoker Adenocarcinoma kras mt (classic)</td>
<td>EGFR wt</td>
</tr>
<tr>
<td>IV</td>
<td>(Ex)smoker Adenocarcinoma EGFR wt kras wt</td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>Squamous Immune phenotyping</td>
<td>Clinical features</td>
</tr>
<tr>
<td>VI</td>
<td>Large Cell Immune phenotyping</td>
<td>Neuroendocrine</td>
</tr>
<tr>
<td>VII</td>
<td>NSCL Poorly differentiated</td>
<td></td>
</tr>
<tr>
<td>VIII</td>
<td>Small Cell</td>
<td></td>
</tr>
</tbody>
</table>

### The Eight Buckets of Lung Cancer:

**I. EGFR mt+**

**Required:** Activating EGFR mt
- exon 19 del
- exon 21 L858R

**Supportive:** Adenocarcinoma (almost invariable)
kras wt (absolutely)
TTF1+ (almost invariable?)
Papillary/non-invasive adenocarcinoma especially
Less likely in acinar/solid variants of adenocarcinoma

**Associated:**
- Asian, Female, Never/light ex-smoker
- 65% of the “IPASS population”
- Often EGFR FISH +ve (but not always)

**Comment:**
- ≤ 15% of “Western” lung ca are “never/light ex-smokers”
- ≥ 30% of these will be EGFR mt
- Can occur in Caucasians, Males
- 50% of Asian ‘smoking adenoc’ are EGFR mt
- 8% of Western “smoking adenoc” are EGFR mt
- Half the Western EGFR mt pts are (ex)smokers, half are never/light ex-smokers

**Target:** Activating EGFR mt

**Rule:** Best option in 1st line is EGFR-TKI (gefitinib)
(EGFR-TKI work in any line)
- Target therapy to chemotherapy, penetration preferred
Adenocarcinoma, histology. Papillary adenocarcinoma. Tumor cells are growing along the surface of branching fibrovascular cores. The tumor cells have moderate amount of cytoplasm and small to medium sized nucleoli (case showed EGFR mutation).

Motoi et al, 2008

Adenocarcinoma, histology. Micropapillary adenocarcinoma. Tumor cells are growing in small clusters without fibrovascular cores (case showed EGFR mutation).

Motoi et al, 2008
Table 2. Comparison of EGFR and KRAS mutations with clinicopathologic features of adenocarcinoma

<table>
<thead>
<tr>
<th>Variables</th>
<th>n</th>
<th>EGFR Mutations (%)</th>
<th>p</th>
<th>KRAS Mutations (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>84</td>
<td>28 (33.3)</td>
<td>0.001</td>
<td>14 (15.7)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>131</td>
<td>87 (66.4)</td>
<td></td>
<td>7 (5.3)</td>
<td>0.009</td>
</tr>
<tr>
<td>Smoking history</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NS</td>
<td>131</td>
<td>103 (74.8)</td>
<td>4 (3.8)</td>
<td>11 (85.1)</td>
<td>0.207*</td>
</tr>
<tr>
<td>PS</td>
<td>18</td>
<td>11 (61.1)</td>
<td>0.001*</td>
<td>0 (0)</td>
<td>0.002*</td>
</tr>
<tr>
<td>EX</td>
<td>28</td>
<td>19 (67.9)</td>
<td>0.001*</td>
<td>4 (21.4)</td>
<td>0.003*</td>
</tr>
<tr>
<td>SM</td>
<td>58</td>
<td>11 (19.6)</td>
<td>0.001*</td>
<td>11 (19.6)</td>
<td>0.003*</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td>0.001</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Differentiation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WD</td>
<td>86</td>
<td>66 (76.4)</td>
<td>4 (4.7)</td>
<td>10 (11.7)</td>
<td>0.104</td>
</tr>
<tr>
<td>MD</td>
<td>88</td>
<td>49 (56.3)</td>
<td>0.266*</td>
<td>10 (11.6)</td>
<td>0.104</td>
</tr>
<tr>
<td>PD</td>
<td>41</td>
<td>11 (26.8)</td>
<td>0.001*</td>
<td>7 (17.3)</td>
<td>0.037*</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>0.001*</td>
<td>0.004</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: NS, never smoker; PS, past smoker; EX, ex smoker; SM, smoker; WD, well differentiated; MD, moderately differentiated; PD, poorly differentiated.

*p values were calculated comparing the two groups of the variables.
TTF-1 as a Master Regulator of Peripheral Parenchyma

- Transcription factor for functional molecules, including surfactant proteins
- A cellular series unit, supplied from common stem cells
- Impaired development of peripheral lung parenchyma despite intact bronchial trees in KO mice

EGFR Mutation and Variables

EGFR Mutation and TRU

Logistic regression model to estimate significant factors related with EGFR mutation.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Category</th>
<th>Odds ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Median</td>
<td>0.508 (0.296 - 0.908)</td>
<td>0.0863</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>0.67 (0.253 - 1.870)</td>
<td>0.4207</td>
</tr>
<tr>
<td>Smoking status</td>
<td>Non-smoker</td>
<td>4.518 (1.654 - 12.108)</td>
<td>0.0033</td>
</tr>
<tr>
<td></td>
<td>Smoker</td>
<td>0.493 (0.174 - 0.893)</td>
<td>0.4637</td>
</tr>
<tr>
<td>Histology</td>
<td>BAC/Non-BAC</td>
<td>0.493 (0.174 - 0.893)</td>
<td>0.4637</td>
</tr>
<tr>
<td>Stage</td>
<td>Early-stage (EA)</td>
<td>0.993 (0.497 - 9.933)</td>
<td>0.9831</td>
</tr>
<tr>
<td>Cellular lineage</td>
<td>TRU-type/Non-TRU-type</td>
<td>16.593 (4.628 - 65.593)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

Plenary Lecture I

Short Summary

- Terminal Respiratory Unit Lineage
  - EGFR mutation
  - HER2 mutation
  - BRAF mutation
  - EML4-ALK fusion
  - EGFR amplification
  - TTF-1 amplification
  - KRAS mutation
  - LKB1 mutation

IPASS Study design

Patients
- Age ≥ 18 years
- Life expectancy ≥ 12 weeks
- Adenocarcinoma
- Never smokers or light ex-smokers
- PS 0-2
- Stage IIIb/IV
- Measurable disease

Endpoints
- Primary
  - Progression free survival (non-inferiority)
- Secondary
  - Objective response rate
  - Quality of life
  - Disease related symptoms
  - Overall survival
  - Safety and tolerability
- Exploratory
  - Biomarkers
    - EGFR mutation
    - EGFR gene copy number
    - EGFR protein expression

Gefitinib
250 mg/day
1:1 randomization

Carboplatin AUC 5 or 6 and Paclitaxel 200mg/m² 3 weekly

*Never smokers: < 100 cigarettes in lifetime; light ex-smokers: stopped ≥ 15 years ago and smoked ≤ 10 pack yrs.
Carboplatin/paclitaxel was offered to gefitinib patients upon progression
PS, performance status; EGFR, epidermal growth factor receptor

Objective response rate in EGFR mutation positive and negative patients

<table>
<thead>
<tr>
<th>Overall response rate (%)</th>
<th>Gefitinib</th>
<th>Carboplatin / paclitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=132)</td>
<td>47.3%</td>
<td>71.2%</td>
</tr>
<tr>
<td>(n=129)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Gefitinib
- EGFR M+ odds ratio (95% CI) = 2.75
  (1.65, 4.60), p=0.0021
- EGFR M- odds ratio (95% CI) = 1.04
  (0.91, 1.27), p=0.8033

Carboplatin/paclitaxel
- EGFR M+ odds ratio (95% CI) = 2.01
  (0.91, 4.43), p=0.083
- EGFR M- odds ratio (95% CI) = 0.79
  (0.37, 1.70), p=0.5498

Odds ratio >1 implies greater chance of response on gefitinib

Mok et al, Chicago 2008
RECENTLY REPORTED PHASE III STUDIES OF GEFTINIB AS 1ST LINE IN SELECTED A-NSCLC PATIENTS: EGFR mt + SUBSET

<table>
<thead>
<tr>
<th></th>
<th>IPASS</th>
<th>First-Signal</th>
<th>NEJ002</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS HR p</td>
<td>0.48</td>
<td>0.613</td>
<td>0.36</td>
</tr>
<tr>
<td>ORR (CT/G) p</td>
<td>0.0001</td>
<td>0.002</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chemo</td>
<td>C/P</td>
<td>G/C</td>
<td>C/P</td>
</tr>
<tr>
<td>Author</td>
<td>Mok et al 2009</td>
<td>Lee et al 2009</td>
<td>Kobayashi et al 2009</td>
</tr>
<tr>
<td>n</td>
<td>132/129</td>
<td>26/16</td>
<td>98/100</td>
</tr>
</tbody>
</table>

DISTRIBUTION AND EFFECT OF EGFR MUTATION TYPES

<table>
<thead>
<tr>
<th></th>
<th>ASIAN STUDIES</th>
<th>NON-ASIAN STUDIES</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IPASS</td>
<td>V-15-32</td>
</tr>
<tr>
<td>n</td>
<td>261</td>
<td>31</td>
</tr>
<tr>
<td>Exon 19 del</td>
<td>54%</td>
<td>42%</td>
</tr>
<tr>
<td>Exon 21 point</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L858R</td>
<td>43%</td>
<td>52%</td>
</tr>
<tr>
<td>L861Q</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>Exon 20, T790M</td>
<td>4%</td>
<td>3%</td>
</tr>
</tbody>
</table>

IPASS: Exon 19, del PFS HR 0.337 (p<0.001)
Exon 21, L858R PFS HR 0.553 (p=0.010)

The Eight Buckets of Lung Cancer:
II. Never-Smoker EGFR wt

Required: EGFR wt
          Neverlight ex-smoker
          Adenoca

Supportive: Absence of a classical (transversion) kras mt

Associated: Female predominantly
           Asian > Caucasian
           40% of "IPASS population"
           70% of Western neverlight ex-smokers

Comment: May be EGFR FISH+ or -
         15% may exhibit a non-classical (transition, G>T/A) kras mt
         Is this a homogeneous group?
         Is there a specific histological pattern? (Not mucinous BAC)

Target: Driver(s) unknown (Yras in these 15%?)

Rule: EGFR-TKI totally inactive
      Chemotherapy best choice
      Less chemosensitive than EGFR mt+
      Cisplatin/pemetrexed gold standard
      Even if EGFR FISH +ve, still no benefit from EGFR-TKI
The 9th Annual Meeting of Korean Association for Clinical Oncology

EGFR mutation positive status and clinical characteristics

<table>
<thead>
<tr>
<th>% of samples EGFR mutation positive</th>
<th>Overall EGFR mutation positive rate = 59.7% (201 / 437)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>49.6</td>
</tr>
<tr>
<td>Female</td>
<td>93.0</td>
</tr>
<tr>
<td>P.S. ≤1</td>
<td>60.5</td>
</tr>
<tr>
<td>P.S. &gt;1</td>
<td>57.1</td>
</tr>
<tr>
<td>Never smoked</td>
<td>89.7</td>
</tr>
<tr>
<td>Light smoker</td>
<td>41.9</td>
</tr>
<tr>
<td>Locally advanced</td>
<td>57.8</td>
</tr>
<tr>
<td>Metastasis</td>
<td>68.2</td>
</tr>
<tr>
<td>Age &lt;60 yrs</td>
<td>58.7</td>
</tr>
<tr>
<td>Age ≥60 yrs</td>
<td>88.6</td>
</tr>
</tbody>
</table>

Mok et al, Chicago 2008

Objective response rate in EGFR mutation positive and negative patients

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</tr>
<tr>
<td></td>
<td>(1.65, 4.60), p=0.0001</td>
</tr>
<tr>
<td>47.3% (n=129)</td>
<td>EGFR M+ odds ratio (95% CI) = 0.04</td>
</tr>
<tr>
<td></td>
<td>(0.51, 0.27), p=0.0013</td>
</tr>
<tr>
<td>1.1% (n=91)</td>
<td></td>
</tr>
<tr>
<td>23.5% (n=85)</td>
<td></td>
</tr>
</tbody>
</table>

Odds ratio > 1 implies greater chance of response on gefitinib

Mok et al, Chicago 2008
EGFR wt (lung)
kras wt (lung and ampulla)

The Eight Buckets of Lung Cancer:
III. The 'Smoking Adenos' with ras mutations

Required:
- Ex-smoker
- Adenocarcinoma
- kras mt (classical transversion type; G→T or G→C)

Supportive:
- EGFR wt
- Poorly differentiated
- SAC mucinous are 66% ras mutated
- Any type of adenoc except non-mucinous

Association:
- Likely not benefited from prior adjuvant chemotherapy
- TTF-1 status uncertain

Comment:
- 40% of Western 'smoking adenos' are kras mt
- 17% of Asian 'smoking adenos' are kras mt
- Mutually exclusive with EGFR mt
- Kras mt cases may/may not be EGFR FISH+
- Almost never identified as a distinct subgroup

Target:
- kras a driver but remains undruggable

Rule:
- Resistant to EGFR-TKI
- Still responsive to chemotherapy
- May accelerate on EGFR-TKI ("active harm")
- Cisplatin/pemetrexed gold standard

Adenocarcinoma
### Table 1
Summary of EGFR and K-ras Mutations in IHC Subtypes

<table>
<thead>
<tr>
<th>IHC Subtype</th>
<th>No. of Cases</th>
<th>EGFR Mutation</th>
<th>K-ras Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-invasive</td>
<td>50</td>
<td>22 (32.1)</td>
<td>10 (16)</td>
</tr>
<tr>
<td>Invasive</td>
<td>17</td>
<td>0 (3.5)</td>
<td>13 (70)</td>
</tr>
<tr>
<td>Non-invasive</td>
<td>10</td>
<td>15 (73)</td>
<td>NA</td>
</tr>
<tr>
<td>Invasive</td>
<td>5</td>
<td>0 (0)</td>
<td>NA</td>
</tr>
<tr>
<td>Present study</td>
<td>17</td>
<td>15 (88)</td>
<td>8 (47)</td>
</tr>
<tr>
<td>Invasive</td>
<td>9</td>
<td>2 (22)</td>
<td>8 (88)</td>
</tr>
</tbody>
</table>

**Notes:**
- IHC: immunohistochemical carcinoma.
- EGFR: epidermal growth factor receptor.
- K-ras: Kirsten rat sarcoma viral oncogene.
- NA: not available.

### Table 2
Comparison of EGFR and K-ras mutations with clinicopathologic features of adenocarcinoma

<table>
<thead>
<tr>
<th>Variables</th>
<th>EGFR Mutation</th>
<th>K-ras Mutation</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>28 (33.3)</td>
<td>14 (15.7)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>87 (65.4)</td>
<td>7 (5.3)</td>
<td></td>
</tr>
<tr>
<td>Smoking history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NS</td>
<td>111</td>
<td>63 (48.9)</td>
<td>4 (3.6)</td>
</tr>
<tr>
<td>PS</td>
<td>18</td>
<td>11 (61.1)</td>
<td>0.267</td>
</tr>
<tr>
<td>EX</td>
<td>28</td>
<td>10 (35.7)</td>
<td>0.001</td>
</tr>
<tr>
<td>SM</td>
<td>58</td>
<td>11 (19.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>Overall</td>
<td>196</td>
<td>46 (23.6)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

**Notes:**
- NS: non-smoker.
- PS: past smoker.
- EX: ex-smoker.
- SM: smoker.
Results: Outcomes based on **EGFR** and **KRAS** status

Clinical Outcomes: Time to Progression

<table>
<thead>
<tr>
<th></th>
<th>EGFR+ / KRAS WT</th>
<th>EGFR WT / KRAS +</th>
<th>EGFR+ / KRAS+</th>
<th>EGFR WT / KRAS WT</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>40</td>
<td>41</td>
<td>83</td>
<td>3</td>
</tr>
<tr>
<td>Median TTP</td>
<td>15.1</td>
<td>3.1</td>
<td>3.1</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

![Graph showing probability of progression-free survival over time](image)

**TABLE 1. ANALYSES OF KRAS MUTATIONS AND EFFICACY OF EPIDERMAL GROWTH FACTOR RECEPTOR TYROSINE KINASE INHIBITORS IN NON-SMALL CELL LUNG CANCER**

<table>
<thead>
<tr>
<th>Author</th>
<th>Drugs</th>
<th>Patients Tested for KRAS Mutations (Total Number Mutant)</th>
<th>Response Rate in KRAS Mutant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pao (2)</td>
<td>Gefitinib/erlotinib</td>
<td>59 (9)</td>
<td>0%</td>
</tr>
<tr>
<td>Jackman (47)</td>
<td>Erlotinib</td>
<td>41 (6)</td>
<td>0%</td>
</tr>
<tr>
<td>Zhu (48)</td>
<td>Erlotinib</td>
<td>206 (30)</td>
<td>5%</td>
</tr>
<tr>
<td>Miller (49)</td>
<td>Erlotinib</td>
<td>80 (18)</td>
<td>0%</td>
</tr>
<tr>
<td>Massarelli (50)</td>
<td>Gefitinib/erlotinib</td>
<td>70 (16)</td>
<td>0%</td>
</tr>
<tr>
<td>Hinrich (51)</td>
<td>Gefitinib</td>
<td>138 (36)</td>
<td>1%</td>
</tr>
<tr>
<td>Hinrich (52)</td>
<td>Gefitinib</td>
<td>152 (12)</td>
<td>0%</td>
</tr>
<tr>
<td>Han (53)</td>
<td>Gefitinib</td>
<td>69 (9)</td>
<td>0%</td>
</tr>
<tr>
<td>Van Sandwijk (54)</td>
<td>Gefitinib</td>
<td>13 (3)</td>
<td>0%</td>
</tr>
<tr>
<td>Fujimoto (55)</td>
<td>Gefitinib</td>
<td>31 (7)</td>
<td>0%</td>
</tr>
<tr>
<td>Felip (56)</td>
<td>Erlotinib</td>
<td>39 (7)</td>
<td>0%</td>
</tr>
</tbody>
</table>


**Surveillance: Relapse**

August 2008
After 2 cycles Pemetrexed

September 2008

CT pre- & post- 4 cycles of Pemetrexed

July 2008  November 2008

Needle biopsy, July 2007
Plenary Lecture I

Forward

\[ \text{GTTGGAGCCTGGGTGCAGGT} \]

\[ \text{Gly12Cys} \]

Reverse

\[ \text{CTGGCTACAGCCGACGCTCGTA} \]

\[ \text{CCAAGCA} \]

Results:
KRAS Gly12Cys
(\(\sim\)30% mutant)

TRIBUTE: by k ras

BR.21

KRAS Mutation

\[ \text{Median 95\% CI} \]

- Erlotinib: 3.7 (1.9 to 7.9)
- Placebo: 7.0 (1.7 to 19.5)

HR = 1.67 (0.82 to 3.40)

\[ P = .3096 \]

Zhu C-Q et al. J Clin Oncol 2008; 26: p 4
The 9th Annual Meeting of Korean Association for Clinical Oncology

**SWOG 0023 Overall Survival**

Overall Survival From Randomization

- Median FU time: 27 months
- Median survival: 12 months

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Events</th>
<th>%</th>
<th>70%</th>
<th>80%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gefitinib</td>
<td>119</td>
<td>59</td>
<td>76%</td>
<td>80%</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>125</td>
<td>54</td>
<td>76%</td>
<td>81%</td>
<td></td>
</tr>
</tbody>
</table>

**P = .01**

*...the inferior survival observed in the Gefitinib arm raises the possibility of a discontinuous effect***

Kelly et al J Clin Oncol 2009

---

**Is there a survival benefit with Tarceva in current/ex-smokers?**

**Current/ex-smokers**

- HR = 0.9 (0.7–1.0), p = 0.141
- Tarceva (n=358)
- Placebo (n=187)

**Never smokers**

- HR = 0.42 (0.28–0.64), p = 0.001
- Tarceva (n=164)
- Placebo (n=42)

*Log-rank test Treatment interaction test p = 0.02 (significant)*

---

**BR 21 Subgroup Analysis**

- HR = 0.86, p = 0.141
- HR = 0.42, p = 0.001
- HR = 0.71, p < 0.0001

Current/ex-smokers

Never smokers

Whole population
**BR21: Is there a survival advantage in 2nd or 3rd line for squamous-cell carcinoma (almost all smokers)?**

HR=0.67, p=0.0007

**BR21 Subgroup Analysis:**
**Exposing the Hidden Subgroup**

HR=0.67, p=0.0007

HR = 0.94-1.00

? =

HR=0.86, p=0.141

Squamous patients (Smokers)

Non-squamous Smokers

All Smokers


**Iressa Survival Evaluation in Lung Cancer, ISEL**

- 1692 patients in 210 centres across 28 countries

Patients with:
- Histologically / cytologically confirmed NSCLC
- Locally advanced or metastatic disease
- 1 or 2 prior CT regimens
- Intolerant to most recent CT regimen or progression ≤30 days of last CT cycle

Randomisation (2:1 ratio)

Gefitinib (250mg/day) + BSC

Placebo + BSC

End points
- Primary:
  - Survival
  - Secondar:
    - TTP
    - ORR
    - QoL, symptoms
    - Safety
- Exploratory:
  - Tumour biomarker analysis (eg EGFR)

CT, chemotherapy; BSC, best supportive care; TTP, time to treatment failure; ORR, objective response rate; QoL, quality of life

The 9th Annual Meeting of Korean Association for Clinical Oncology

**Outcome by Ethnicity and Smoking Status (survival)**

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Never smoked</th>
<th>Smokers</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oriental</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=141</td>
<td>0.26 (0.06, 0.61)</td>
<td>0.97 (0.06, 0.09)</td>
<td>0.26 (0.06, 0.09)</td>
</tr>
<tr>
<td>Non-oriental</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=374</td>
<td>0.43 (0.06, 0.61)</td>
<td>0.96 (0.06, 0.09)</td>
<td>0.43 (0.06, 0.09)</td>
</tr>
<tr>
<td>All</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=515</td>
<td>0.43 (0.06, 0.61)</td>
<td>0.96 (0.06, 0.09)</td>
<td>0.43 (0.06, 0.09)</td>
</tr>
</tbody>
</table>

- Improvement over placebo (or no treatment)!
- The improvement in Asians is ALL driven by non-smokers!!
- Asian smokers did not benefit as compared to PLACEDO, or no treatment.

Source: AstraZeneca filed for MRCA, Japan

**The Eight Buckets of Lung Cancer:**

IV. The ‘smoking adenos’ with neither mutation

**Required:**

- AdenoCa
- EGFR wt
- kras wt
- [Expt](smoker

**Supportive:**

- ± 55% of Asian smoking adenos
- ± 50% of Western smoking adenos
- TTF-1 status uncertain

**Comments:**

- May or may not be EGFR FISH+
- The driver is unknown

**Target:**

- Not known

**Rule:**

- EGFR TKIs – modest activity at most (SD)
- Chemotherapy probably active
- Crizotinib/pemetrexed gold standard

**Estimated Genomic Probabilities (2)**

<table>
<thead>
<tr>
<th>Country</th>
<th>n</th>
<th>AdenoCa</th>
<th>AdenoCa</th>
<th>Never smoker</th>
<th>Never smoker</th>
<th>Never smoking Adeno</th>
<th>Never smoking Adeno</th>
<th>Ever smoking Adeno</th>
<th>Ever smoking Adeno</th>
<th>Ever smoking Adeno</th>
<th>Ever smoking Adeno</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>JAPAN</td>
<td>253</td>
<td>1.3%</td>
<td>44%</td>
<td>6%</td>
<td>80%</td>
<td>17%</td>
<td>26%</td>
<td>57%</td>
<td>43%</td>
<td>43%</td>
<td>43%</td>
<td></td>
</tr>
<tr>
<td>JAPAN</td>
<td>118</td>
<td>8.5%</td>
<td>63%</td>
<td>2%</td>
<td>8%</td>
<td>17%</td>
<td>?</td>
<td>9%</td>
<td>?</td>
<td>9%</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>JAPAN</td>
<td>82</td>
<td>6%</td>
<td>46%</td>
<td>73%</td>
<td>7%</td>
<td>33%</td>
<td>?</td>
<td>9%</td>
<td>?</td>
<td>9%</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>BRAZIL</td>
<td>65</td>
<td>10%</td>
<td>58%</td>
<td>6%</td>
<td>64%</td>
<td>17%</td>
<td>30%</td>
<td>52%</td>
<td>52%</td>
<td>52%</td>
<td>52%</td>
<td></td>
</tr>
<tr>
<td>TAIWAN</td>
<td>60</td>
<td>61%</td>
<td>56%</td>
<td>84%</td>
<td>9%</td>
<td>9%</td>
<td>9%</td>
<td>9%</td>
<td>9%</td>
<td>9%</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>HONG KONG</td>
<td>241</td>
<td>106%</td>
<td>96%</td>
<td>63%</td>
<td>96%</td>
<td>10%</td>
<td>16%</td>
<td>31%</td>
<td>62%</td>
<td>43%</td>
<td>43%</td>
<td></td>
</tr>
<tr>
<td>USA</td>
<td>80</td>
<td>24%</td>
<td>56%</td>
<td>6%</td>
<td>27%</td>
<td>10%</td>
<td>11%</td>
<td>11%</td>
<td>11%</td>
<td>11%</td>
<td>11%</td>
<td></td>
</tr>
<tr>
<td>Australia</td>
<td>26</td>
<td>24%</td>
<td>64%</td>
<td>6%</td>
<td>24%</td>
<td>13%</td>
<td>11%</td>
<td>11%</td>
<td>11%</td>
<td>11%</td>
<td>11%</td>
<td></td>
</tr>
</tbody>
</table>

26
Results: Outcomes based on **EGFR and KRAS** status

**Clinical Outcomes: Response**

<table>
<thead>
<tr>
<th></th>
<th>EGFR+ / KRAS WT</th>
<th>EGFRWT / KRAS+</th>
<th>EGFRWT / KRAS WT</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>46</td>
<td>41</td>
<td>93</td>
</tr>
<tr>
<td>CR</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>31</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>SD</td>
<td>14</td>
<td>10</td>
<td>35</td>
</tr>
<tr>
<td>PD</td>
<td>0</td>
<td>18</td>
<td>5</td>
</tr>
<tr>
<td>NR</td>
<td>1</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td><strong>Response Rate</strong></td>
<td>31%</td>
<td>0%</td>
<td>4%</td>
</tr>
</tbody>
</table>

Results: Outcomes based on **EGFR and KRAS** status

**Clinical Outcomes: Time to Progression**

<table>
<thead>
<tr>
<th></th>
<th>EGFR+ / KRAS WT</th>
<th>EGFRWT / KRAS+</th>
<th>EGFRWT / KRAS WT</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>46</td>
<td>41</td>
<td>93</td>
</tr>
<tr>
<td>Median TTP</td>
<td>15.1</td>
<td>3.1</td>
<td>3.1</td>
</tr>
</tbody>
</table>

Results: Outcomes based on **EGFR and KRAS** status

**Clinical Outcomes: Overall Survival**

<table>
<thead>
<tr>
<th></th>
<th>EGFR+ / KRAS WT</th>
<th>EGFRWT / KRAS+</th>
<th>EGFRWT / KRAS WT</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>46</td>
<td>41</td>
<td>93</td>
</tr>
<tr>
<td>Kaplan-Meier</td>
<td>11.8</td>
<td>6.0</td>
<td>6.0</td>
</tr>
</tbody>
</table>

---

27
The 9th Annual Meeting of Korean Association for Clinical Oncology

The Eight Buckets of Lung Cancer: IV. Squamous Carcinoma

Required:
- Squamous differentiation
- Immune phenotyping

Supportive:
- Typical clinical picture
- Absence of EGFR mt
- Absence of kras mt
- Smoking history

Associations:
- COPD
- Male > Female
- High levels of TS

Comment:
- Risk of ILD with EGFR-TKI
- Brivanibamib contra-indicated
- Drivers may be TTS and EGFR over-expression

Target:
- EGFR over-expression in many

Rule:
- Chemotherapy preferred
- Pembrolizumab less active
- EGFR-TKI have activity

Lung Cancer Pathology
Squamous cell ca

Immunohistochemistry of Lung Cancer
- TTF-1
- Surfactant Apoproteins
- Napsin A
- CK 7
- p63
- HMWCK (CK5-6, 34βE12)
- Desmocollin 3

Scagliotti 2009
ASCO 2009 UPDATE

Diagnostic reproducibility of squamous cell carcinoma in the era of histology-directed non-small-cell lung cancer chemotherapy: A large prospective study.
Grillot-Olson JE et al

- Virtual slides 96 surgically resected
- 12 "expert" pathologists and 12 "community" pathologists
- Kappa scores

Diagnostic Categories

<table>
<thead>
<tr>
<th></th>
<th>Full WHO</th>
<th>Simplified WHO</th>
<th>Pragmatic SC/non-SC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expert pathologist</td>
<td>0.3</td>
<td>0.58</td>
<td>0.64</td>
</tr>
<tr>
<td>Community pathologist</td>
<td>0.19</td>
<td>0.36</td>
<td>0.41</td>
</tr>
</tbody>
</table>

- Self rated confidence: high 63%, somewhat 32%, not confident 5%
- Conclusions: Reproducible diagnosis of squamous carcinoma based on H&E is inadequate

J Clin Oncol 27: 15x, 2009 (abstr #008)

Distinct Epidermal Growth Factor Receptor and KRAS Mutation Patterns in Non–Small Cell Lung Cancer Patients with Different Tobacco Exposure and Clinicopathologic Features

Isaac Yee San, Tim1, Lap Ping Chung, Wei Sing Sam1, Boon Wang2, Mary C-M. Wong1, Kok Keong Hu1, Wai K. Lam1, Shiu Wah Chan3, Luc Grand1, John D. Mina1, Ali F. Gasiuk1 and Man P. Wong2


KRAS mutations ... 0/15 squamous carcinomas
The 9th Annual Meeting of Korean Association for Clinical Oncology

**Figure 1**

Comparisons of relative gene expressions between adenocarcinoma and squamous cell carcinoma specimens.

**TS**, thymidylate synthase; **DPD**, dihydropyrimidine dehydrogenase; **TP**, thymidine phosphorylase; **GPRC**,otate phosphoribosyltransferase; **Ad**, adenocarcinoma; **Sq**, squamous cell carcinoma.

Relative expression of TS:
- **Adenocarcinoma**: 1.60 ± 0.86
- **Squamous carcinoma**: 4.33 ± 3.40

Ishihama et al., Jpn J Clin Oncol 2009

### The Eight Buckets of Lung Cancer:
#### VI. Large Cell Carcinoma

**Requirement:**
- Large Cell
- Negative immune phenotyping
- Undifferentiated
- Adequate biopsy

**Supportive:**
-Rare Endocrine features in some

**Association:**
- Smoking
- Highly aggressive
- Inadequate histology

**Comments:**
- A traditional default category
- Ought to shrink
- Probably several entities
- NE features do not predict chemosensitivity
- Molecular biology obscure
- Low TS in some
- High TS in LCNEC
- EGFR int probably do not occur

**Target:**
- Unknown

**Rule:**
- Cisplatin/pemetrexed best in 1st line
- Pemetrexed best in 2nd line

---

### Large Cell Carcinoma

![Large Cell Carcinoma Image]
TOPIC SIX
THE RISING INFLUENCE OF HISTOLOGY IN CHEMOTHERAPY SELECTION

NON-SMALL CELL LUNG CANCER

<table>
<thead>
<tr>
<th>1st generation</th>
<th>2nd generation</th>
<th>3rd generation</th>
</tr>
</thead>
<tbody>
<tr>
<td>cyclophosphamide</td>
<td>ifosfamide</td>
<td>paclitaxel</td>
</tr>
<tr>
<td>doxorubicin</td>
<td>mitomycin C</td>
<td>docetaxel</td>
</tr>
<tr>
<td>cisplatin (low dose)</td>
<td>cisplatin (high dose)</td>
<td>gemcitabine</td>
</tr>
<tr>
<td>vincristine</td>
<td>vinblastine</td>
<td>vinorelbine</td>
</tr>
<tr>
<td>methotrexate</td>
<td>carboplatin</td>
<td>Irinotecan</td>
</tr>
<tr>
<td>etoposide</td>
<td>vindesine</td>
<td></td>
</tr>
</tbody>
</table>

Pemetrexed is 4th generation

Hitting the Wall
First-line chemotherapy options in NSCLC (E1594): comparable efficacy with platinum doublets

Therapeutic plateau: overall survival <12 months

- Cisplatin/paclitaxel
- Cisplatin/gemcitabine
- Cisplatin/docetaxel
- Carboplatin/paclitaxel

R/SCLC = non-small cell lung cancer
Plenary Lecture I

Pemetrexed vs. Docetaxel in 2nd-line NSCLC

Stratified by:
- ECOG PS 0/1 vs. 2
- Stage III vs. IV
- # of prior chemo
- Best response to prior chemo
- Time since last chemo
- Prior platinum
- Prior taxane
- Homocysteine level
- Center

Pemetrexed
500 mg/m² i.v. q3wks (n=283)
(folic acid 350-1,000 µg daily +
vitamin B₁₂, 1,000 µg q 9wks;
dexamethasone 4mg bid on
d-1,d0,d+1)

Docetaxel
75 mg/m² i.v. q3wks (n=288)
(dexamethasone 8 mg bid on
d-1,d0,d+1)

Results of Analyses – Overall Survival

Survival Post Hoc Analysis

<table>
<thead>
<tr>
<th>Efficacy Measure</th>
<th>Total Number of Events</th>
<th>Test for Interaction: Non-Squamous vs Other</th>
<th>Efficacy Statistic</th>
<th>Adenocarcinoma vs Large Cell Lung Cancer</th>
<th>Squamous Cell Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pem (n=178)</td>
<td>Doc (n=178)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pem (n=178)</td>
<td>Doc (n=178)</td>
</tr>
<tr>
<td>OS</td>
<td>373</td>
<td>HR**=0.48, p&lt;0.001</td>
<td>median, months</td>
<td>9.2</td>
<td>8.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6.2</td>
<td>7.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HR** (95% CI)</td>
<td>0.78 (0.92–1.02)</td>
<td>1.36 (1.08–2.68)</td>
</tr>
<tr>
<td>PFS</td>
<td>478</td>
<td>HR=0.56, p&lt;0.001</td>
<td>median, months</td>
<td>3.4</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.5</td>
<td>3.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HR (95% CI)</td>
<td>0.78 (0.82–0.98)</td>
<td>1.49 (1.0–1.96)</td>
</tr>
</tbody>
</table>

WCLC 2007 – Peterson P et al., Abstract # P3-025
JMDB:
Cis/Pem vs. Cis/Gem in First-Line NSCLC: Study Design

Randomization Factors
Stage
Performance status (PS) (0 vs 1)
Gender
Histologic vs cytologic diagnosis
History of brain metastases

Cisplatin 75 mg/m² day 1 +
Pemetrexed 500 mg/m² day 1

Each cycle repeated
every 3 weeks up to 8 cycles

Cisplatin 75 mg/m² day 1 +
Gemcitabine 1250 mg/m² days 1 & 8

Vitamin B<sub>12</sub>, folate, and dexamethasone given in both arms

Cis/Pem: cisplatin/pemetrexed; Cis/Gem: cisplatin/gemcitabine

| Cis/Pem vs. Cis/Gem in First-Line NSCLC: Toxicties and Supportive Care |
|--------------------------|--------------------------|--------------------------|
|                         | Cis/Pem N=839 | Cis/Gem N=830 | p-value |
| Hematologic Grade 3/4 Toxicities* |             |             |         |
| Neutropenia               | 15.1%        | 25.7%        | <0.001  |
| Thrombocytopenia           | 4.1%         | 12.7%        | <0.001  |
| Anemia                    | 5.0%         | 9.9%         | 0.001   |
| Leukopenia                 | 4.0%         | 7.6%         | 0.019   |
| Supportive Care Use†      | N=862        | N=863        | p-value |
| Any transfusion            | 16.4%        | 29.9%        | <0.001  |
| Red blood cell transfusion | 16.1%        | 27.3%        | <0.001  |
| Platelet transfusion       | 1.6%         | 4.5%         | 0.002   |
| Erythropoietin / darbepoietin use | 10.4%    | 18.1%        | <0.001  |
| G-CSF/GM-CSF use           | 3.1%         | 6.1%         | 0.004   |

*Any grade 3/4 Toxicities reported in at least 30% of patients in at least 1 arm are listed
†Supportive Care Use: Adverse events were based on an intent-to-treat population (ITT) and the ITT reflected the ITT groups G-CSF, granulocyte colony stimulating factor; GM-CSF, granulocyte macrophage colony stimulating factor

| Cis/Pem vs. Cis/Gem in First-Line NSCLC: Nonhematologic Toxicities |
|--------------------------|--------------------------|--------------------------|
|                         | Cis/Pem N=839 | Cis/Gem N=830 | p-value |
| Drug-Related Toxicities* |             |             |         |
| Fever (any grade)        | 1.3%         | 3.7%         | 0.002   |
| Grade 3/4 fatigue        | 6.7%         | 4.9%         | 0.143   |
| Grade 3/4 nausea          | 7.2%         | 3.9%         | 0.004   |
| Grade 3/4 vomiting        | 6.1%         | 6.1%         | 1.000   |
| Dehydration (any grade)   | 3.6%         | 2.0%         | 0.075   |
| Alopecia (any grade)      | 11.9%        | 21.4%        | <0.001  |

*Drug-related grade 3/4 toxicities reported in at least 30% of patients in at least 1 arm are listed
Deaths attributed to study drug toxicity were few and were similar between arms:
- 1 patient (1.2%); Cis/Pem, 0 patients (0.0%) for Cis/Gem
Cis/Pem, cisplatin/pemetrexed; Cis/Gem, cisplatin/gemcitabine; CTC, Common Toxicity Criteria
**Cis/Pem vs. Cis/Gem in First-Line NSCLC:**
Efficacy by Histology

<table>
<thead>
<tr>
<th></th>
<th>Median OS, months</th>
<th>Median PFS, months</th>
<th>RR, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cis/Pem</td>
<td>Cis/Gem</td>
<td>Adj. p-value</td>
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<tr>
<td>Adenocarcinoma</td>
<td>12.6</td>
<td>10.9</td>
<td>0.04</td>
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<tr>
<td>n=847</td>
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<tr>
<td>Large Cell</td>
<td>10.4</td>
<td>9.6</td>
<td>0.07</td>
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<tr>
<td>n=153</td>
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<tr>
<td>Other*</td>
<td>8.6</td>
<td>9.2</td>
<td>0.09</td>
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<tr>
<td>n=252</td>
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<td></td>
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<tr>
<td>Squamous</td>
<td>9.4</td>
<td>10.8</td>
<td>0.03</td>
</tr>
<tr>
<td>n=473</td>
<td></td>
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</tbody>
</table>

*Patients with histologic diagnosis did not clearly qualify as adenocarcinoma, large or squamous cell carcinoma.

Cis/Pem, cisplatin/pemetrexed; Cis/Gem, cisplatin/gemcitabine; OS, overall survival; PFS, progression-free survival; RR, response rate.

**Fig. 2** - Survival without grade 3 or 4 drug-related toxicity for patients with non-squamous histology treated with cisplatin and pemetrexed (n = 604) versus cisplatin and gemcitabine (n = 608).

Scaglotti et al. Eur J Cancer 2009; 45: 2268

---

**Survival in Ever-Smokers with Adenocarcinoma**
Survival in Never-Smokers with Adenocarcinoma

Number of Patients Enrolled by Country

<table>
<thead>
<tr>
<th>Country</th>
<th>Sites</th>
<th>Entered</th>
<th>Enrolled country entered</th>
<th>Country</th>
<th>Sites</th>
<th>Entered</th>
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<tbody>
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<td>Argentina</td>
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<td>28</td>
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<td>11</td>
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<td>123</td>
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<td>62</td>
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<td>37</td>
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<td>Netherlands</td>
<td>8</td>
<td>113</td>
<td>110</td>
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<td>Brazil</td>
<td>5</td>
<td>70</td>
<td>62</td>
<td>Poland</td>
<td>4</td>
<td>85</td>
<td>80</td>
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<td>16</td>
<td>Sweden</td>
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<td>35</td>
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<td>France</td>
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<td>62</td>
<td>58</td>
<td>Taiwan</td>
<td>6</td>
<td>80</td>
<td>72</td>
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<td>Germany</td>
<td>28</td>
<td>205</td>
<td>203</td>
<td>Turkey</td>
<td>5</td>
<td>63</td>
<td>62</td>
</tr>
<tr>
<td>Greece</td>
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<td>47</td>
<td>42</td>
<td>UK</td>
<td>7</td>
<td>46</td>
<td>46</td>
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<tr>
<td>Hungary</td>
<td>3</td>
<td>41</td>
<td>38</td>
<td>US</td>
<td>22</td>
<td>132</td>
<td>118</td>
</tr>
<tr>
<td>India</td>
<td>8</td>
<td>160</td>
<td>154</td>
<td>Total</td>
<td>177</td>
<td>1833</td>
<td>1725</td>
</tr>
</tbody>
</table>

Overall Survival – East Asian (Korea and Taiwan only) Nonsquamous Patients

OS Median (95% CI)
- PC (n=47) 21.2 mos (17.1, 25.2)
- GC (n=49) 17.7 mos (11.7, 22.0)

OS Adjusted HR (95% CI)
- PC vs GC 0.70 (0.39, 1.24)
### Survival by Histology and Smoking Status

<table>
<thead>
<tr>
<th>Histology and Smoking Group</th>
<th>Overall Study Population</th>
<th>East Asian (Korea &amp; Taiwan Only)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PC</td>
<td>GC</td>
</tr>
<tr>
<td>All smokers</td>
<td>n=629</td>
<td>n=427</td>
</tr>
<tr>
<td>Median overall survival, mos</td>
<td>10.02</td>
<td>16.25</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.02 (0.91, 1.05)</td>
<td>0.74 (0.37, 1.46)</td>
</tr>
<tr>
<td>Nonsquamous smokers</td>
<td>n=430</td>
<td>n=449</td>
</tr>
<tr>
<td>Median overall survival, mos</td>
<td>10.55</td>
<td>9.79</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.81 (0.69, 0.94)</td>
<td>0.99 (0.25, 3.96)</td>
</tr>
<tr>
<td>Squamous smokers</td>
<td>n=199</td>
<td>n=188</td>
</tr>
<tr>
<td>Median overall survival, mos</td>
<td>5.43</td>
<td>10.94</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.36 (0.30, 1.50)</td>
<td>0.78 (0.23, 2.68)</td>
</tr>
<tr>
<td>All never-smokers</td>
<td>n=126</td>
<td>n=122</td>
</tr>
<tr>
<td>Median overall survival, mos</td>
<td>15.90</td>
<td>15.20</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.00 (0.71, 1.40)</td>
<td>0.73 (0.35, 1.50)</td>
</tr>
<tr>
<td>Nonsquamous never-smokers</td>
<td>n=112</td>
<td>n=105</td>
</tr>
<tr>
<td>Median overall survival, mos</td>
<td>17.12</td>
<td>16.40</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.96 (0.66, 1.39)</td>
<td>0.63 (0.29, 1.37)</td>
</tr>
<tr>
<td>Squamous never-smokers</td>
<td>n=95</td>
<td>n=77</td>
</tr>
<tr>
<td>Median overall survival, mos</td>
<td>12.65</td>
<td>15.26</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>2.51 (0.64, 9.31)</td>
<td>NE*</td>
</tr>
</tbody>
</table>

*NE=Not estimable due to the few deaths.

### Post-discontinuation Therapy with EGFR TKIs

<table>
<thead>
<tr>
<th>Histology Group Receiving PDT</th>
<th>Overall Study Population</th>
<th>East Asian (Korea &amp; Taiwan Only)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PC</td>
<td>GC</td>
</tr>
<tr>
<td>EGFR TKIs*</td>
<td>n=862</td>
<td>n=883</td>
</tr>
<tr>
<td>All histology</td>
<td>26%</td>
<td>23%</td>
</tr>
<tr>
<td>Nonsquamous</td>
<td>28%</td>
<td>27%</td>
</tr>
<tr>
<td>Squamous</td>
<td>19%</td>
<td>11%</td>
</tr>
</tbody>
</table>

*EGFR: Epidermal growth factor receptor; TKIs: tyrosine kinase inhibitors.

- In the overall study population, in the all histology and nonsquamous groups, the use of post-discontinuation EGFR TKIs was similar between treatment arms. In the squamous group, TKI use was slightly higher on the GC arm.
- For the East Asian (Korea and Taiwan only) population, particularly in nonsquamous patients, survival trended in favor of PC over GC despite a higher use of post-discontinuation TKIs on the GC arm.
- In East Asian (Korea and Taiwan only) squamous patients, the higher use of post-discontinuation TKIs observed on the PC arm may help explain the OS results for PC compared to GC in this population.

### “Morphology remains the best biomarker for chemotherapy selection in NSCLC”

Griley-Olson JE et al
J Clin Oncol 27:15s, 2009 (suppl; abstr 8008)
Plenary Lecture I

SATURN: Sequential Tarceva in unresectable NSCLC

Cappuzzo et al. ASCO 2009

SATURN

Brugger et al. ASCO 2009

TOPIC SEVEN
PUTTING IT ALL TOGETHER
Algorithms – 4 different situations

- Biomarkers
  - No
  - Yes

- Maintenance
  - No
  - Yes

<table>
<thead>
<tr>
<th>Current</th>
<th>Transitional</th>
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</thead>
<tbody>
<tr>
<td>Transitional</td>
<td>Imminent Std-of-care</td>
</tr>
</tbody>
</table>

Figure 1

- A - NSCLC Systemic Rx candidate
  - Nonsquamous
    - Adenocarcinoma
      - (Ex) smoker
    - Large Cell
      - Never smoker
  - Squamous

Figure 2

- Squamous
  - 4-6 x cisplatin/gemcitabine ± cetuximab
    - 1st line
      - Erlotinib
      - Docetaxel
    - 2nd line
      - Docetaxel
    - 3rd line
      - Erlotinib

Note: The author has occasionally found ECF (epirubicin/cisplatin/5FU/cv) to be effective in the 2nd line, irrespective of histology.
Maintenance but no biomarkers

Figure 2

Squamous

4-6 x cisplatin/gemcitabine ± cetuximab

Chemotherapy or Anti-EGFR (erlotinib or cetuximab)

Erlotinib Docetaxel

No standard No standard

1st line 2nd line 3rd line

Maintenance

Note: The author has occasionally found ECF (erlotinib/cisplatin/SFU cix) to be effective in the 3rd line, irrespective of histology.

No maintenance, no biomarkers

Figure 3

Large Cell

4-6 x cisplatin/pemetrexed (± bevacizumab)

erlotinib OR docetaxel OR pemetrexed

No standard

1st line 2nd line 3rd line

Biomarkers but no maintenance chemotherapy

Figure 5

Adenoacarcinoma

EGFR wt

4-6 x cisplatin/pemetrexed ± bevacizumab

Chemotherapy

EGFR mut

Pemetrexed (platinum) ± pemetrexed

Continuous EGFR TKI

No standard

Maintenance

Note: The author has occasionally found ECF (erlotinib/cisplatin/SFU cix) to be effective in the 3rd line, irrespective of histology.
The 9th Annual Meeting of
Korean Association for Clinical Oncology

Plenary Lecture II

좌장: 노정실(국립암센터)
Progress in Oncology PARP Inhibition

John E. Pippen Jr, MD, FACP
Baylor-Sammons Cancer Center, Dallas, Texas

In the United States in 1971, president Richard Nixon declared “war on cancer”, and stated that cancer would be conquered by 1976. Since that time, some argue that there has actually been little progress in regards to treating people with advanced stages of the disease. This is despite the millions of dollars spent every year on research. In 2009 and beyond, hopefully with the definition of better targets in cancer cells, more progress will be made in regards to the treatment of advanced cancer. At the 2009 American Society of Clinical Oncology Annual Meeting, Dr. J. O'Shaughnessy presented a study involving the PARP inhibitor BSI-201 on behalf of herself, Pippen J, Osborne C, et al and US Oncology research. This new class of therapy targets an enzyme that keeps a cancer’s DNA repair system functional. The 120 subjects in this randomized phase II study were women with advanced triple negative breast cancer. In this presentation, it was noted that the addition of intravenously administered BSI-201 to the chemotherapy doublet carboplatin/gemcitabine showed a clinical benefit rate of 62%, compared to 21% for the chemotherapy drugs alone (p=0.0002). Overall response rate was 48% compared to 16% in the chemotherapy only arm. Even though a relatively small number of subjects were in the study, a survival advantage was noted for the group receiving BSI-201. Median overall survival was 9.2 months in the BSI-201 arm, compared to 5.7 months in the chemotherapy only arm (p=0.0005). Addition of the new drug added no toxicities. This has led to USON Research undertaking a phase III trial using the same drugs in a larger number of subjects with advanced triple negative breast cancer. Other investigators reported success with the oral PARP inhibitor olaparib at the same meeting. Studies such as these show that measurable progress in being made in regards to finding unique targets in advanced cancer, and bringing these agents to the clinic where they will help our patients.
Symposium

End-of-Life Decisions

최장: 김철수 (인하의대)
사회적 합의에 근거한 무의미한 연명치료의 중단

허 대석

한국보건의료연구원, 서울대학교 의과대학 내과학교실

인공호흡기와 같은 연명장치는 급성질환으로 생명의 위협을 받는 환자들의 목숨을 구하는 의학 발전의 큰 성과였다. 그러나 이 장치가 자연스럽게 임종을 맞이해야만 만성질환자에게까지 널리 적응되면서, 의미 있는 삶이 아니라 고통 받는 기간을 연장시키는 상황이 발생하고 있다. 우리나라에는 1년에 25만 명이 사망하고 있는데, 대부분 병원에서 임종을 맞이하게 되면서, 정도의 차이는 있지만, 임종의 전 단계에서 어느 선까지 연명치료를 해야 할 것인가를 결정하는 과정에서 의료진과 환자 가족들이 갈등을 겪는 일이 현저한 현장에서 점점 증가하고 있다.

2009년 5월 대법원의 판결은 다음과 같은 의미를 지니고 있다.

첫째, 의학적 결정을 하는 주체의 변화이다. 전통적으로 의학적 결정은 의사가 하고 환자가 동의하는 방식이었으나, 이번 판결은 연명장치를 거부한다는 환자의 자기결정권을 의사의 기술적 판단보다 우선하고 있다.

둘째, 의료행위의 적절성을 판단하는 기준에 의료기술뿐만 아니라 환자의 가치도 고려하고 있다. 이번 사건에서 해당병원은 8%의 확률로 의식을 회복할지도 모른기에 때문에 연명치료를 중단할 수 없다고 주장했으나, 다른 병원의 의사들은 회생가능성이 희박하다는 의견을 제시하여 기술적 판단이 애매한 상태였다.

기술적 판단이 불확실한 상황에 대하여, 법원은 환자가 무의미한 연명치료는 원하지 않았다는 생명에 대한 관심 가치를 최종 결정의 근거로 삼고 있다. 연명치료와 같은 문제에서 기술적 판단이 한계에 부딪혀 상황에서 ‘가치’를 고려한 결정했다는 것은, 선진국들이 수십 년의 논의를 거쳐 확정한 무의미한 연명치료의 중단에 관한 제도를 우리나라도 본격적으로 논의하는 단계에 이르렀음을 의미한다.

셋째, ‘무의미한 연명치료의 중단’은 연명치료를 거부할 수 있는 환자의 권리 향상에서 논의하는 것이 필요하며, 심폐소생술금지(do-not-resuscitate; DNR)도 심폐소생술을 거부할 수 있는 환자의 권리의 시작에서 접근하는 것이 적절하다. 연명치료중단에 관여한 의사를 살인방조죄로 처벌받는 보라매 병원 사건의 영향으로, 이 논의가 중환자 치료 중에 발생할 수 있는 의사들의 책임문제를 면해주기 위한 것처럼 오해되고 있는 측면이 있다. 이같은 논의의 본질은 환자의 자기결정권에 관한 것이다.

1. 풍미있는 죽음?

임종을 어떻게 맞이하는 것이 적절한 것인지 쉽게 이해하기 어렵다. 그러나, 어떤 죽음이 적절하지 않은 모습인지에 대한 생각은 쉽게 정리될 수 있다. 월리엄 폴의 소설 ‘오두막(The Shack)’에는 연쇄 살인범이 10살 앞서 어린 딸을 납치하여 살해한 뒤, 시체조차도 찾지 못하게 된 아버지의 처참한 심정을 기술하고 있다. 우리나라도 일련의 살인범들의 피해자들이, 가족들에 엄청난 고통과 상처를 남겼을 뿐이다.

이같은 경우, 대부분의 가족이 원하는 것은 피해당자자의 시신이라도 찾아서 편안히 장례를 치려고 노력한 것이다. 그러나, 임종과정에서 환자 및 가족들이 받게 되는 고통의 상처를 자유발견을 원한다는 쾌락은 알고 있는 죽음의 예를 통하여, 편안한 죽음의 의미를 정리해보면 Table 1과 같다.
무의미한 연명치료가 왜 문제를 야기하는지? 무의미한 연명치료과정은 대부분 특수한 연명장치를 사용하게 된다. 심폐소생술, 인공호흡기 등이 이에 속한다. 이 같은 특수연명장치를 사용할지라도 회생시키는 것이 아니고, 연명하는 것이 주된 목적이다. 이때, 연명된 생명기간의 대부분은 의미있는 시간이기보다는 불필요한 고통을 추가로 받는 시간이 되기 쉽다. 존엄한 죽음의 의미를 고려하여, 무의미한 연명치료의 문제점과 대안을 정리하면 Table 1과 같다.

<table>
<thead>
<tr>
<th>무의미한 연명치료가 존엄한 죽음을 방해하는 이유</th>
<th>존엄한 죽음</th>
<th>존엄한 죽음</th>
<th>무의미한 연명치료</th>
<th>대안</th>
</tr>
</thead>
<tbody>
<tr>
<td>육신</td>
<td>고통 속에 죽음을 맞이함.</td>
<td>육체적으로 죽음과 동일하게</td>
<td>심폐소생술, 인공호흡기 등으로</td>
<td>환화의료 가중시킴</td>
</tr>
<tr>
<td></td>
<td>편안히 잠들지 못함</td>
<td>불필요한 고통을 입는</td>
<td>임종환자에게</td>
<td></td>
</tr>
<tr>
<td>영적</td>
<td>고통과 상처를 교복하고</td>
<td>마음에 걸림이 없는</td>
<td>연명장치에 의존하여 종환자실에서</td>
<td></td>
</tr>
<tr>
<td></td>
<td>마음에 걸림이 없이</td>
<td>임종을 받아야함</td>
<td>보낼 때, 환자의 일생에서 발생 호스피스</td>
<td></td>
</tr>
</tbody>
</table>

Table 1. 무의미한 연명치료가 존엄한 죽음을 방해하는 이유

2. 다른 나라의 규범

Table 2. 무의미한 연명치료에 대한 입장 요약

<table>
<thead>
<tr>
<th>미국의사협회(AMA)</th>
<th>가톨릭 교회</th>
<th>Protean Lutheran Church</th>
<th>대한: 안녕향</th>
<th>일본후생노동성: 종합기의료의 결정프로세스에 관한 가이드라인</th>
</tr>
</thead>
<tbody>
<tr>
<td>암력자</td>
<td>반대</td>
<td>반대</td>
<td>반대</td>
<td>(−)</td>
</tr>
<tr>
<td>의사조력자</td>
<td>반대</td>
<td>반대</td>
<td>반대</td>
<td>(−)</td>
</tr>
<tr>
<td>무의미한 연명치료의 중단</td>
<td>인정</td>
<td>인정</td>
<td>인정</td>
<td>인정</td>
</tr>
<tr>
<td>사전의료지시</td>
<td>인정</td>
<td>인정</td>
<td>인정</td>
<td>인정</td>
</tr>
</tbody>
</table>

(−) 명시적 표현이 없는 상태

3. 사회적 합의

한국보건의료연구원에서 무의미한 연명치료의 중단과 관련하여 논의회, 학회/단체 대표자회의, 연명치료 실태 조사, 설문조사 등을 통하여 연구한 결과 다음과 같은 합의사항과 추가 합의가 필요 한 사항으로 2009년 9월 정리하였다.

<대상>
① 회생 가능성이 없는 말기 환자에서 단순히 임종기간만을 연장하는 무의미한 연명치료는 중단 될 수 있다.
② 회사상태에서 연명치료를 계속하는 것은 적절하지 않으며, 관련 법률의 정비가 필요하다.

<절차>
③ 말기 상태의 환자들은 담당 주치의와 해당 분야 전문의 등 2인 이상이 수행한다.
음식물의 양/수액공급과 통증조절 등 기본적인 의료행위는 유지되어야 한다.

말기 환자에게 사전의료지시서에 대한 정보를 제공하고, 그 내용을 이해하고 동의할 수 있도록 설명할 책임이 있다. 사전의료지시서는 환자가 입원한 병원에서 작성하는 것이 가장 이상적이다. 

의학적 판단 및 가치 판단 등에서 불확실성으로 인한 문제를 최소화하기 위한 안전장치로 병원윤리위원회의 역할이 중요하다. 각 병원에서의 의료윤리 및 생명존중의 위자문제 등이 포함된 병원윤리위원회가 이 같은 역할을 할 수 있도록 병원윤리위원회에 대한 지원균등 및 제도적 지위의 부여가 필요하다.

<내용>

영양/수액공급과 통증조절 등 기본적인 의료행위는 유지되어야 한다.

말기 환자가 사전의료지시서를 통해 심폐소생술이나 인공호흡기 거부의사를 밝힐 경우 중단 될 수 있다. 

심폐소생술이나 인공호흡기 외의 연명치료에 대해서도 말기 환자는 사전의료지시서를 통하여 본인의 의사를 피력할 수 있으며, 의료진의 의학적 판단과 환자의 가치관을 고려하여 결정한다.

안락사 및 의사조력자살은 반대한다.

<제도>

무의미한 연명치료의 중단에 대한 법적 근거가 마련되어야 한다. 

판련 제도가 사회에 정착되기 위해서는 사회보장제도의 강화, 호스피스완화의료제도에 대한 지원 등 사회경제적 지원 확대가 함께 이루어져야 한다.

추가적인 논의가 필요하고 다음과 같다.

1) 의사 결정 능력이 없는 말기 환자에서 발생한연명치료와 관련된 문제에 대해서는 다음과 같은 의견이 제안되어 합의가 필요하다.

   1) 환자의 입장에서 의사결정과 가족이 함께 결정하는 의견
   2) 병원윤리위원회 또는 법원의 판단을 받아야한다는 의견

2) 지속적 식물상태 환자는 다양한 의학적 상황을 내포하고 있어 일반적인 규정으로 인정 혹은 금지를 명시하는 것은 혼란을 야기할 우려가 있으므로 사회적 합의가 필요하다.

무의미한 연명치료를 유보하는 것과 이미 적용중인 연명치료를 중지하는 것은 윤리적으로 법적으로 동일하다. 사회의 수용성을 고려한 합의가 필요하다.

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Table 3. 무의미한 연명치료의 중단: 사회적 합의와 쟁점

<table>
<thead>
<tr>
<th>사회적 합의</th>
<th>쟁점 사항</th>
</tr>
</thead>
<tbody>
<tr>
<td>대상</td>
<td>파송, 말기 상태</td>
</tr>
<tr>
<td>정체</td>
<td>사전의료지시서(가족결정)</td>
</tr>
<tr>
<td>병원윤리위원회</td>
<td></td>
</tr>
<tr>
<td>공증의무화 반대</td>
<td></td>
</tr>
<tr>
<td>내용</td>
<td>영양공급, 통증조절 유지</td>
</tr>
<tr>
<td>인공호흡기, 심폐소생술 중단 가능</td>
<td></td>
</tr>
<tr>
<td>제도</td>
<td>법적 근거 마련</td>
</tr>
</tbody>
</table>

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4. 향후 논의 방향에 대한 제언

Fig. 1. Advance care planning.

Fig. 2. 연명치료 논의와 의료자원의 균형적 배분

참 고 문 헌

연명치료 중단 대법원 판결의 의의와 과제
박 형욱
연세대학교 의과대학 의료법윤리학과

I. 서 론

2009. 5. 21. 대법원 전원합의체는 우리나라에서는 처음으로 무의미한 연명치료 중단 판결을 선고하였다. 이는 그 필요성을 인지하기 시작한 국민여론에 대한 답변에 동시에 보라매병원 사건이 후속되어 온 의료현장에서의 갈등에 대한 답변이기도 한다. 그러나 인공호흡기 제거 후 환자가 자발호흡을 유지하면서 생명을 이어가고 있어 판결에 대한 논란이 계속되고 있다. 아래에서는 세브란스병원 사건의 경과(III), 판결의 주요 내용(IV), 의의(V), 그리고 문제점과 과제(VI)를 차례로 검토하고자 한다. 본론에 앞서 보라매병원 판결과 미국의 카렌 퀸란 판결을 비교하여 문제 해결을 위한 접근방법을 탐색해 보고자 한다. 이는 실제 소송에서 연세대학교 세브란스병원이 소송의 승부로 끝지지 않게 연명치료 중단의 일반적 요건 혹은 절차가 중요하다는 점을 강조하며 제시한 내용에 기초하고 있다.

II. 보라매병원 판결과 카렌 퀸란 판결

보라매병원 사건에서 대법원은 환자 가족의 요구에 따라 환자를 퇴원시킨 의사에게 살인방조죄를 선고한 바 있다. 이후 형사처벌의 위험에 직면한 의사들은 연명치료 중단을 극도로 피하게 되었고 이와 관련된 분쟁이 끊이지 않고 있다. 이러한 현상에 대하여 일부 법조인들은 의사들이 보라매병원 판결을 오해하고 있다고 말한다. 즉 보라매병원 판결은 회생가능성이 있는 사례이기 때문에 이 판결을 회생가능성이 없는 경우에까지 확대적용하여서는 안 된다는 것이다. 물론 의사들이 보라매병원 판결을 제대로 이해하지 못한 부분도 있다.

그러나 문제의 본질은 거기에 있는 것이 아니다. 왜냐하면 이분법적 개념의 세계가 아닌 현실 세계에서 회복가능성 혹은 생존가능성은 개념적으로 추정할 수밖에 없으며 일반적 요건이 이에 따라 변함에도 불구하고 명확하게 제시되어 있지 않다. 더 중요한 것은 보라매병원 판결에는 몇 %의 회복가능성 혹은 생존가능성이 있을 때 연명치료를 중단할 수 있는지 혹은 어떤 절차를 거쳐야 할지가 명확하게 제시되지 않는다는 점이다.

보라매병원 판결은 현실 세계에 사는 의사들의 법적인 불안 상태에 폭로하려는 것이 아님이다. 환자의 가족들도 마찬가지이다. 이처럼 일반적 요건 혹은 절차의 제시 없이 구체적 타당성을 과도한 판결은 우리 사회에 커다란 후유증을 남긴 것이다.

반면 카렌 퀸란 사건에서 미국 뉴저지주 대법원은 무의미한 연명치료 중단에 대한 명확한 절차적 기준을 제시함으로써 사회적 혼란을 최소화하고 있다. 1975년 21세였던 카렌 퀸란은 지속적 식물상태가 되었으며 담당 의사의 인공호흡기를 제거하자 퇴원시킨 카렌의 후견인과 가족이 이에 항의한 경우 그들은 법원의"
리위원회 혹은 유사한 기구에 자문을 구할 수 있다. 그리고 거기에도 동일한 절론에 도달한다면 생명유지장치를 제거할 수 있으며 그 행위로 인하여 후견인, 의사, 병원 등 관련자들은 누구도 민사상, 형사상 책임을 지지 않는다...."

우리나라의 학자들은 대체로 이 카렌 퀸란 판결을 프라이버시권에 근거하여 환자의 죽음권을 제거하고, 그 행위로 인하여 후견인, 의사, 병원 등 관련자들은 누구도 민사상, 형사상 책임을 지지 않는다...."

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기록을 살펴보면 환자의 의식 상태는 계속 악화하여, 이에 따라 환자의 전신상태도 계속 악화하고 있다.

"...2008. 10. 15. 현재 환자는 중환자실에 누워 있으며 인공호흡기에 전적으로 의지하여 호흡을 하고 있었음. 환자는 스스로 호흡을 trigger 할 수 없었음. 환자는 자발적으로 눈을 떼어 자유롭게 시선을 변화시킬 수 없었음. 환자는 자발적으로 눈을 떼어 자유롭게 시선을 변화시킬 수 없었음. 환자는 자발적으로 눈을 떼어 자유롭게 시선을 변화시킬 수 없었음. 환자는 자발적으로 눈을 떼어 자유롭게 시선을 변화시킬 수 없었음. 환자는 자발적으로 눈을 떼어 자유롭게 시선을 변화시킬 수 없었음. 환자는 자발적으로 눈을 떼어 자유롭게 시선을 변화시킬 수 없었음. 환자는 자발적으로 눈을 떼어 자유롭게 시선을 변화시킬 수 없었음. 환자는 자발적으로 눈을 떼어 자유롭게 시선을 변화시킬 수 없었음. 환자는 자발적으로 눈을 떼어 자유롭게 시선을 변화시킬 수 없었음. 환자는 자발적으로 눈을 떼어 자유롭게 시선을 변화시킬 수 없었음. 환자는 자발적으로 눈을 떼어 자유롭게 시선을 변화시킬 수 없었음. 환자는 자발적으로 눈을 떼어 자유롭게 시선을 변화시킬 수 없었음. 환자는 자발적으로 눈을 떼어 자유롭게 시선을 변화시킬 수 없었음. 환자는 자발적으로 눈을 떼어 자유롭게 시선을 변화시킬 수 없었음. 환자는 자발적으로 눈을 떼어 자유롭게 시선을 변화시킬 수 없었음. 환자는 자발적으로 눈을 떼어 자유롭게 시선을 변화시킬 수 없었음. 환자는 자발적으로 눈을 떼어 자유롭게 시선을 변화시킬 수 없었음. 환자는 자발적으로 눈을 떼어 자유롭게 시선을 변화시킬 수 없었음. 환자는 자발적으로 눈을 떼어 자유롭게 시선을 변화시킬 수 없었음. 환자는 자발적으로 눈을 떼어 자유롭게 시선을 변화시킬 수 없었음. 환자는 자발적으로 눈을 떼어 자유롭게 시선을 변화시킬 수 없었음. 환자는 자발적으로 눈을 떼어 자유롭게 시선을 변화시킬 수 없었음. 환자는 자발적으로 눈을 떼어 자유롭게 시선을 변화시킬 수 없었음. 환자는 자발적으로 눈을 떼어 자유롭게 시선을 변화시킬 수 없었음. 환자는 자발적으로 눈을 떼어 자유롭게 시선을 변화시킬 수 없었음. 환자는 자발적으로 눈을 떼어 자유롭게 시선을 변화시킬 수 없었음. 환자는 자발적으로 눈을 떼어 자유롭게 시선을 변화시킬 수 없었음. 환자는 자발적으로 눈을 떼어 자유롭게 시선을 변화시킬 수 없었음. 환자는 자발적으로 눈을 떼어 자유롭게 시선을 변화시킬 수 없었음. 환자는 자발적으로 눈을 떼어 자유롭게 시선을 변화시킬 수 없었음. 환자는 자발적으로 눈을 떼어 자유롭게 시선을 변화시킬 수 없었음. 환자는 자발적으로 눈을 떼어 자유롭게 시선을 변화시킬 수 없었음. 환자는 자발적으로 눈을 떼어 자유롭게 시선을 변화시킬 수 없었음. 환자는 자발적으로 눈을 떼어 자유롭게 시선을 변화시킬 수 없었음. 환자는 자발적으로 눈을 떼어 자유롭게 시선을 변화시킬 수 없었음. 환者は 자발적으로 눈을 떼어 자유롭게 시선을 변화시킬 수 없었음. 환자는 자발적으로 눈을 떼어 자유롭게 시선을 변화시킬 수 없었음. 환자는 자발적으로 눈을 떼어 자유롭게 시선을 변화시킬 수 없었음. 환자는 자발적으로 눈을 떼어 자유롭게 시선을 변화시킬 수 없었음. 환자는 자발적으로 눈을 떼어 자유롭게 시선을 변화시킬 수 없었음. 환자는 자발적으로 눈을 떼어 자유롭게 시선을 변화시킬 수 없었음. 환자는 자발적으로 눈을 떼어 자유롭게 시선을 변화시킬 수 없었음. 환자는 자발적으로 눈을 떼어 자유롭게 시선을 변화시킬 수 없었음. 환자는 자발적으로 눈을 떼어 자유롭게 시선을 변화시킬 수 없었음. 환자는 자발적으로 눈을 떼어 자유롭게 시선을 변화시킬 수 없었음. 환자는 자발적으로 눈을 떼어 자유롭게 시선을 변화시킬 수 없었음. 환자는 자발적으로 눈을 떼어 자유롭게 시선을 변화시킬 수 없었음. 환자는 자발적으로 눈을 떼어 자유롭게 시선을 변화시킬 수 없었음. 환자는 자발적으로 눈을 떼어 자유롭게 시선을 변화시킬 수 없었음. 환자는 자발적으로 눈을 떼어 자유롭게 시선을 변화시킬 수 없었음. 환자는 자발적으로 눈을 떼어 자유롭게 시선을 변화시킬 수 없었음. 환자는 자발적으로 눈을 떼어 자유롭게 시선을 변화시킬 수 없었음. 환자는 자발적으로 눈을 떼어 자유롭게 시선을 변화시킬 수 없었음. 환자는 자발적으로 눈을 떼어 자유롭게 시선을 변화시킬 수 없었음. 환자는 자발적으로 눈을 떼어 자유롭게 시선을 변화시킬 수 없었음. 환자는 자발적으로 눈을 떼어 자유롭게 시선을 변화시킬 수 없었음. 환자는 자발적으로 눈을 떼어 자유롭게 시선을 변화시킬 수 없었음. 환자는 자발적으로 눈을 떼어 자유롭게 시선을 변화시킬 수 없었음. 환자는 자발적으로 눈을 떼어 자유롭게 시선을 변화시킬 수 없었음. 환자는 자발적으로 눈을 떼어 자유롭게 시선을 변화시킬 수 없었음. 환자는 자발적으로 눈을 떼어 자유롭게 시선을 변화시킬 수 없었음. 환자는 자발적으로 눈을 떼어 자유롭게 시선을 변화시킬 수 없었음. 환자는 자발적으로 눈을 떼어 자유로...
유서 제출 당시 환자의 상태는 다음과 같다.

"...환자는 저산소성 뇌손상으로 대뇌의 인지 기능이 상실되고 의식이 없고 의사소통이 불가능한 지속적 식물상태이며 더 나아가 자발호흡이 거의 없는 상태로서 인공호흡기의 도움 없이는 호흡을 유지할 수 없는 상태이다. 그러나 통증에 대하여 반응하며 두 눈의 동공이 확대되지 않은 상태로 고정되어 있으며 뇌간반사 중 안구두부반사, 구역반사 등이 살아 있고 뇌파검사상 평탄뇌파가 아니라 제한적으로 복추적으로 여전히 보존되어 있다. 또한 비 경험한 상태와 동일한 상태로 잘 유지되고 있으며 향상되지 않아도 되고, 제반 등 활동성과 비교적 잘 유지되는 상태로서 환자의 기대 생존기간은 적어도 4개월은 될 것으로 추정된다..."

대법원은 사안의 중요성을 감안하여 같은 해 4.30. 공개변론을 열었으며 같은 해 5.21. 상고를 기각하였다.

이후 연세대학교 세브란스병원은 병원윤리위원회를 개최하고 같은 해 6.23. 환자의 인공호흡기를 제거하였다. 그러나 그 후 환자는 자발호흡을 유지하면서 2009. 8. 현재 특별한 두려움 없이 혼란, 평온, 호흡을 유지하고 있어 판결에 대한 논란이 계속되고 있다.

IV-1. 1심 판결의 주요내용

첫째, 1심 판결은 환자(원고 1)의 청구를 인용하였지만 환자의 자녀들(원고 2, 3, 4, 5)의 청구는 기각하였다.

즉 환자의 자녀들인 원고 2, 3, 4, 5는 환자에게 인공호흡기를 계속하여 부착하는 것은 자신들에 게 경제적-정신적으로 큰 고충을 가하고 인간적으로의 존엄과 가치 발생추구권, 평등권, 양심의 자유권, 건강권, 재산권 등을 철저함으로 자신들도 독자적으로 인공호흡기의 제거를 구할 수 있는 권리를 가진다고 주장하였다. 그러나 1심 판결은 치료의 중단은 환자의 자기결정권 행사에 근거하는 것이므로 환자의 가족은 경제적-정신적으로 고통을 받고 있다고 하더라도 그에 관한 입법이 없는 한 독자적으로 환자에 대한 인공호흡기의 제거를 청구할 권리를 가진다고 보기 어렵다고 판시하고 있다.

둘째, 1심 판결은 퇴비적치료 중단의 일반적 요건과 관련하여 환자를 '응급의료에 관한 법률'의 규율을 받는 응급환자로서 인정하고 동법 제10조의 응급의료를 중단할 수 있는 정당한 사유가 있는지에 대해 정당하고 지적할 수 있는 기준으로 구성되어 있다.

즉 어떠한 치료를 중단함으로써 환자가 곧바로 사망에 이르게 되는 경우 특별한 사정이 없는 한 그 환자는 응급환자라고 할 것이고 이에 대하여 치료의 중단은 생명보호의 원칙 및 역법상의 사상형태, 피고팀에 의한 사전의 과정을 거쳐야 할 필요가 있다. 따라서 인공호흡기를 제거하면 곧바로 사망에 이르게 되는 상황에 있는 환자의 경우 의사는 인공호흡기를 제거하는 환자의 요구에 원칙적으로 응할 의무가 없다. 그러나 의료의료소의 식물상태로 인공호흡기를 의료하여 생명을 유지하고 있는 환자는 1) 치료가 계속되더라도 환자가 의의상이 없어 치료가 의학적으로 무의미하고, 2) 그 치료중단 의사는 체계적십상의 전문가의 의사는 제한되어야 하며 의사는 환자의 지속적치료를 제거 요구를 거부할 수 없다고 볼 수 상당하며 이는 응급의료중단의 정당한 사유가 있는 것으로 의사는 의료의료소의 책임을 부담하지 않는다는 것이다.

또한 1심 판결은 환자의 의사적 의사외의 의학적 판단에 대한 판단은 환자의 의사를 담당한 병

3) 이 소송에서 원고는 환자(원고 1)를 포함하여 환자의 자녀 4명(원고 2, 3, 4, 5) 중 5명이다. 환자는 사상 상 소송을 제기할 수 없는 상태에 이르기 때문에 다른 원고이며 환자의 자녀 중 한 명(원고 4)이 환자의 독립자리

4) 연세대학교 세브란스병원은 응급의료법의 목적은 정상적인 치료가 시작되어 환자의 생명을 방지할 보증인을 부담하게 될 의사가 정례적인 치료에 따라 환자의 생명을 짐작적으로 보호하기 위한 것이므로 환자는 이미 정상적인 치료가 개시된 의료법상의 일반적 의무이지 응급의료법상의 의무는 아니라고 주장하였다.
원 뿐만 아니라 제3의 중립적 의료기관에 의한 의학적 진단 토대로 규범적으로 판단되어야 한다고 판시하고 있음 뿐 병원윤리위원회 등을 연금하고 있지 않고 있으며 의료현장에서의 자율적 해결을 염두에 두고 있지 않다.

셋째, 1심 판결은 이 사건에 관한 구체적 판단과 관련하여 환자의 진료기록, 진료기록 감정의사, 신체감정의사의 감정에 기초하여 환자가 의식을 회복하고 인공호흡기 등의 일시적인 도움 없이 생존이 가능한 상태가 될 가능성이 없으므로 환자에 대한 인공호흡기 부착행위는 의학적으로 무의미하며 환자의 자녀들인 원고 2, 3, 4, 5가 작성한 경위서와 사위의 증언에 기초하여 환자의 인공호흡기 제거 의사가 추정되므로 연세대학교 세브란스 병원은 환자의 인공호흡기제거 요구에 응할 무가 있다고 판시하고 있다.

Ⅳ-2. 항소심 판결의 주요 내용

항소심 판결은 피고의 항소를 기각하였는 바 결론은 1심과 동일하지만 판결의 주요 논리나 개념에는 다소 다른 점이 있다.

첫째, 항소심 판결은 연세대학교 세브란스병원의 주장과 받아들여 연명치료를 받고 있는 환자는 연명치료의 철저로 인한 생명의 급박한 위험으로 벗어나 더 이상 응급환자의 지위에 있지 않고 통상적인 의료행위의 대상으로 전환할 것으로 볼 수 있다고 인정하였으며 환자가 의식을 회복하고 인공호흡기 제거 의사가 추정된 경우에 의한 자가결정권의 행사에 의해 곧바로 가능하다고 판시하고 있다.

둘째, 항소심 판결은 연명치료 중단의 요건과 관련하여 1심 판결보다 더 구체화하여 1) 환자가 회생가능성 없는 비가역적 사망과정에 진입한 경우, 2) 환자의 진정하고 합리적인 치료중단 의사가 있으며(혹은 추정적 의사가 인정되며) 3) 중단을 구하는 치료행위의 내용에 환자의 고유의 본질과 일상적인 진료 등은 포함될 수 없으며 4) 의사의 의학적 중단의 시행 등을 요건으로 제시하고 있다.

셋째, 항소심 판결은 이 사건에 관한 구체적 판단과 관련하여 1심과 거의 동일한 판시를 하고 있다. 또한 항소심은 환자의 의사추정과 관련하여 원고에 대한 연명치료의 중단은 일반인의 도덕관념이나 사회적 태당성의 관점으로 보더라도 합리성이 있다고 판시하고 있다.

항소심 판결의 특징은 다음과 같다. ① 1심은 치료의 의학적 무의미성이라는 가치계급을 사용한 반면 항소심은 회생가능성 없는 비가역적 사망과정에 진입한 경우를 대상으로 해석적 통용을 사용하고 있다. 이는 독일 판례를 차용한 것으로 판단된다. 다만 환자가 의식을 회복할 수 있는 자가결정권의 행사에 대하여는 구체적으로 개념을 정의하고 있는 바 없다. ② 회생가능성 없는 비가역적 사망과정에 진입한 상태를 판단할 주체에 대하여 환자가 의식을 회복할 수 있는 자가결정권의 행사에 대하여는 구체적으로 정의하고 있는 바 없다. 이에 따라 의료기관은 이를 반영하여 제3의 중립적 의료기관에 의한 자가결정권의 행사에 대한 판단도 필요하다고 판시하였다. 다만 의료행위의 내용에 대한 심의는 종합적인 진료 전반을 평가하여 판단하여야 한다. ③ 중단을 구하는 의료행위의 내용에 관련하여 환자의 고유의 본질과 일상적인 진료 등은 포함될 수 없으며 4) 의사의 의학적 중단의 시행 등을 요건으로 제시하고 있다.

대법원은 우선 의료계약의 본질에 비추어 환자가 그 진료행위의 중단을 요구할 경우에 원칙적으로 의료인은 이를 받아들여서 다른 적절한 진료방법이 있는지를 강구하여야 한다. 생명권은 한계로 규정된 모든 기본권의 전체로서 환자의 생명과 직접되는 진료행위를 중단할 것인지 여부는 극히 제한적으로 신중하게 판단하여야 한다고 판시하고 있다. 이에 대법원은 환자가 회복불가능한 사망 단계에 이른 후 진료중단의 자기결정권을 행사하는 것으로 인정되는 경우 특별한 사정이 없는 한
연명치료의 중단이 허용될 수 있으며 원심에서 최고위법원이나 법률위법이 없다며 상고를 기각하였다.

첫째, 대법원은 회복불가능한 사망의 단계에 이르렀을 경우에 대비하여 미리 의료인에게 자신의 연명치료 거부 내지 중단에 관한 의사를 발한 경우를 말한다고 판시한 후 사전의료지시서의 요건을 구체적으로 적시하고 있다. 의사결정능력이 있는 환자가 의료인으로부터 직접 충분한 의학적 정보를 제공받은 후 그 것을 바탕으로 자신의 고유한 가치관에 따라 진지하게 구체적인 진료행위에 관한 의사를 결정하여야 하며 이와 같은 과정이 환자 자신이 직접 의료인을 상대로 하여 작성한 서면이나 진료기록 등에 의하여 진료 중단 시점에서 명확하게 입증할 수 있어 사전의료지시서로서의 구속력을 인정할 수 있다는 것이다. 반면 환자 본인이 작성한 문서라도 위의 요건을 충족하지 못하는 경우 환자의 의사를 추정할 수 있는 객관적인 자료의 하나일 뿐이라는 것이다. 물론 대법원은 사전의료지시서가 없는 경우 환자의 연명치료 중단 의사를 추정할 수 있으며 그것은 객관적으로 이루어져야 한다고 판시하고 있다.

둘째, 대법원은 환자가 직접 입원한 경우 평가된 경우에 대비하여 미리 의료인에게 자신의 연명치료 거부 내지 중단에 관한 의사를 발한 경우를 말한다고 판시한 후 사전의료지시서의 요건을 구체적으로 적시하고 있다. 의사결정능력이 있는 환자가 의료인으로부터 직접 충분한 의학적 정보를 제공받은 후 그 것을 바탕으로 자신의 고유한 가치관에 따라 진지하게 구체적인 진료행위에 관한 의사를 결정하여야 하며 이와 같은 과정이 환자 자신이 직접 의료인을 상대로 하여 작성한 서면이나 진료기록 등에 의하여 진료 중단 시점에서 명확하게 입증할 수 있어 사전의료지시로서의 구속력을 인정할 수 있다는 것이다. 반면 환자 본인이 작성한 문서라도 위의 요건을 충족하지 못하는 경우 환자의 의사를 추정할 수 있는 객관적인 자료의 하나일 뿐이라는 것이다. 물론 대법원은 사전의료지시서가 없는 경우 환자의 연명치료 중단 의사를 추정할 수 있으며 그것은 객관적으로 이루어져야 한다고 판시하고 있다.

셋째, 대법원은 환자가 직접 입원한 경우 평가된 경우에 대비하여 미리 의료인에게 자신의 연명치료 거부 내지 중단에 관한 의사를 발한 경우를 말한다고 판시한 후 사전의료지시서의 요건을 구체적으로 적시하고 있다. 의사결정능력이 있는 환자가 의료인으로부터 직접 충분한 의학적 정보를 제공받은 후 그 것을 바탕으로 자신의 고유한 가치관에 따라 진지하게 구체적인 진료행위에 관한 의사를 결정하여야 하며 이와 같은 과정이 환자 자신이 직접 의료인을 상대로 하여 작성한 서면이나 진료기록 등에 의하여 진료 중단 시점에서 명확하게 입증할 수 있어 사전의료지시로서의 구속력을 인정할 수 있다는 것이다. 반면 환자 본인이 작성한 문서라도 위의 요건을 충족하지 못하는 경우 환자의 의사를 추정할 수 있는 객관적인 자료의 하나일 뿐이라는 것이다. 물론 대법원은 사전의료지시서가 없는 경우 환자의 연명치료 중단 의사를 추정할 수 있으며 그것은 객관적으로 이루어져야 한다고 판시하고 있다.

넷째, 대법원은 환자 측이 직접 법원에 소를 제기한 경우가 아니라면, 환자가 회복불가능한 사망의 단계에 이르렀는 경우, 원심사건의 학문적 지식로서 진료 기록 감정의 결과를 바탕으로 하는 사전의료지시서의 구속력을 인정한 경우에 법리오해 등의 위법이 없다고 판시하고 있다.

다섯째, 대법원은 환자 측이 직접 법원에 소를 제기한 경우가 아니라면, 환자가 회복불가능한 사망의 단계에 이르렀는 경우, 원심사건의 학문적 지식로서 진료 기록 감정의 결과를 바탕으로 하는 사전의료지시서의 구속력을 인정한 경우에 법리오해 등의 위법이 없다고 판시하고 있다.

셋째, 대법원은 환자가 직접 입원한 경우 평가된 경우에 대비하여 미리 의료인에게 자신의 연명치료 거부 내지 중단에 관한 의사를 발한 경우를 말한다고 판시한 후 사전의료지시서의 요건을 구체적으로 적시하고 있다. 의사결정능력이 있는 환자가 의료인으로부터 직관 충분한 의학적 정보를 제공받은 후 그 것을 바탕으로 자신의 고유한 가치관에 따라 진지하게 구체적인 진료행위에 관한 의사를 결정하여야 하며 이와 같은 과정이 환자 자신이 직접 의료인을 상대로 하여 작성한 서면이나 진료기록 등에 의하여 진료 중단 시점에서 명확하게 입증할 수 있어 사전의료지시로서의 구속력을 인정할 수 있다는 것이다. 반면 환자 본인이 작성한 문서라도 위의 요건을 충족하지 못하는 경우 환자의 의사를 추정할 수 있는 객관적인 자료의 하나일 뿐이라는 것이다. 물론 대법원은 사전의료지시서가 없는 경우 환자의 연명치료 중단 의사를 추정할 수 있으며 그것은 객관적으로 이루어져야 한다고 판시하고 있다.

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대법원 판결의 의의는 다음과 같이 세 가지로 요약할 수 있다.

첫째, 대법원이 처음으로 연명치료 중단의 일반적 요건 혹은 절차를 제시하였다는 점이다. 항소심에서 서울고등법원은 연명치료 중단의 일반적 요건을 실시하였고 언론은 처음으로 '존엄사 가이드라인'이 나왔다고 보도하기 시작하였다. 즉 사회적 의제가 연명치료 중단 '정의' 여부에서 연명치료 중단의 '일반적 요건 혹은 절차로 재설정된 것이다. 더 나아가 대법원은 '회복불가능한 사망의 단계'라는 요건을 구체적으로 제시하고 있다. 본래대법원 판결 이후 사법적으로 인정받을 수 있는 연명치료 중단 기준을 알지 못한 채 불안하게 의사결정이 이루어졌던 의료현장에서는 중요한 의의를 갖는 부분이다.

둘째, 대법원이 처음으로 구속력을 인정할 수 있는 사전의료지시서의 요건을 구체적으로 제시하였다는 점이다. 연세대학교 세브란스병원은 법제화 이전이라도 대법원이 사전의료지시서의 중요성은 인정한다는 점을 강조하였으나 대법원은 단순한 언급을 넘어 구체적으로 구속력을 인정할 수 있는 사전의료지시서의 요건을 구체적으로 제시한 것이다. 따라서 의료현장에서 이러한 기준에 맞추어 사전의료지시서가 작성된다면 환자의 자기결정권 보장이 더욱 확보해질 수 있을 것이다.

셋째, 대법원은 연명치료 중단의 구체적 기준에 대해 특정한 요건을 제시하였다는 점이다. 법률에 의하면 특정한 경우에만 연명치료 중단이 가능하므로, 이에 따르면 의료현장에서 이러한 기준에 따라 사전의료지시서가 제출되어야 한다는 것이다. 그러나 대법원은 이러한 구체적인 기준이 아닌 경우에도 사전의료지시서의 작성을 강조하였다. 즉 사전의료지시서는 환자의 생명을 구하기 위한 미처 내린 지시가 되는 것이며, 이에 따라 의료진은 환자의 평가가 정확해야 한다는 점도 강조하였다.

VI. 대법원 판결의 문제점과 과제

먼저 독일의 판례와 비교하여 이번 대법원 판결은 전반적으로 조잡하다. 독일의 판례는 환자가 비역적 사망과정에 진입한 경우 환자의 의사와 무관하게 진행을 중단할 수 있으며 그 전의 의료적 인적 판단에 따라 병원의 가장 중요하다고 판단하고 있다. 다만 지속적 식물상태에서는 비역적 사망과정에 진입한 경우로 보며, 그 이유는 구체적인 판단에 따라 환자의 생명이 위축된 경우에 해당한다. 이는 독일의 판례의 '비역적 사망과정'에 진입하기 전후의 진료중단을 다르게 설정하고 있다. 이는 환자의 자기결정권을 존중하고 동시에 의료의 전문적 판단 권한을 존중할 수 있는 장점이 있다. 반면 대법원 판결은 '회복불가능한 사망의 단계'를 독일의 판례의 '비역적 사망과정'에 진입한 경우보다 더 넓게 설정한 후 진료중단에는 환자의 자기결정권이 요구되며 판단하고 있다. 판결의 구체적 문제점은 다음과 같다.

첫째, 대법원 판결의 '환자의 신체 상태에 비추어 짧은 시간 내에 사망에 이를 수 있을 경우'라는 요건이 구체적으로 무엇을 의미하는 것인지 그리고 이 요건에서 이 요건이 충족될 수 있는지 문제가 된다.

연세대학교 세브란스병원은 상고이유서에서 현재도 환자의 기대 생존 기간은 적어도 4개월은 될 것으로 추정되며 비역적 사망과정에 진입하였다고 볼 수 있으며, 다른 원인을 설계하더라도 인공호흡기 의존상태를 중시하여 환자가 비역적 사망과정에 '진입'하였다고 판단하였을 수 있으나, 만일 그렇다면 ① 일상적 진료에 특별한 진료의 구별기준이 무엇인지, ② 인공호흡기 가 입증 작품과 달리 특별한 진료에 해당하는 것인지, ③ 특별한 진료에 의하면 생존이 유지되는 경우에는 기대 생존 기간이 있겠지만, 따라서 보는 것인지 등으로 판결이 구체화되어야 함을 최소화할 수 있다고 주장하였다.
원심과 달리 대법원은 ‘회복불가능한 사망의 단계’의 의미를 구체적으로 설명하면서 ‘환자의 신체 상태에 비추어 짧은 시간 내에 사망을 이룰 수 있음을 명백한 경우’라고 적시하고 있다. 그러나 이소송에서 환자의 상태는 이에 해당한다고 본 수 없다. 위 판결의 소소의견에서 대법원이 안대희, 대법관 양창수, 대법관 김능환 역시 이와 동일한 의견을 표명하고 있다. 다만 대법원 김지형, 대법관 차한성 역시 사망의 시간적 근접성으로 진료가 의학적으로 무의하다거나 진료의 중단을 정당화하기 주는 것은 아니며 호흡기능을 구체적으로 살펴본 경우에는 회복불가능한 사망의 단계에 진입한 것으로 보아야 한다는 보충의견을 제시하고 있다. 그러나 이러한 취지라면 "환자를 치료하여 생존할 수 있고"라는 시간적 요소를 다소 완화하여 판시하는 것이 실제적 의미에 부합하며 혼란을 줄일 수 있었다.

한편 회복불가능한 사망의 단계와 관련하여 대법원 안대희 대법관은 "환자를 계속적으로 진료하여 옴으로써 환자의 상태를 직접적으로 얻은 자료에 의하여 가장 잘 알고 있을 담당 의무의 의견은, 비록 그가 소송당사자의 일방에 속하여 일하는 경우라고 하더라도, 다른 특별한 사정이 없는 한, 담당 의료기록만을 통하여 환자의 상태에 접근한 다른 전문가의 견해에 비해 그에 일정한 무게를 두지 않을 수 있으며 구체적으로 이 사건에서 환자를 치료하여 온 담당의 사가 환자의 현재 상태를 기준으로 하더라도 그 기대여명이 적어도 4개월 이상이라고 판단하고 있는 점 등에 비추어, 환자가 회복불가능한 사망의 단계에 있다고 결사리 단정할 수는 없다는 의견을 밝히고 있다. 일부 학자들은 이 사건에서 대법원이 담당의사의 의견을 배척하였는 바 법원이 더 큰 논증의무를 부담함에도 판결문에 찾아볼 수 없다는 점을 배제하기도 한다.

이와 관련하여 연세대학교 세브란스병원은 상고이유서에서 다음과 같이 주장하였다. "감정 의사의 의견은 특정 시점에서 환자의 상태를 보고 그 이전의 진료기록을 참고하여 판단하는 것으로 감정 의사는 잘못된 환자의 상태에 대하여는 알 수 없으며, 임상적으로 환자의 상태를 보고 판단하는 담당 의사보다 환자의 상태를 정확히 판정하기 어렵다는 점에서 복구불가능한 사망단계는 원칙적으로 담당 의사의 견해를 존중하고 이를 복구한 윤리위원회와 같은 기구에서 검증하도록 하되, 의료 과실 소송이 발생하는 등 환자 및 가족의 신뢰가 깨어진 경우 외에도 의료 기관의 의무를 첨이므로 얻은 명확한 근거가 미흡한 경우 외에도 의허의 의사의 판단을 존중하여 온다. 문제로 이 사건에서 환자의 기대생존기간에 대한 판단은 감정 의도의 견해는 담당 의무의 견해보다 담당 의무의 견해가 더 정확하였다. 그럼에도 불구하고 대법원 판결은 논증이 논증의무를 이행하지 않았다는 주장을 내세웠다. 왜냐하면 대법원은 인공호흡기에 의존하는 경우 환자가 인공호흡기에 의존하지 않으므로 생명을 회복할 수 있는 상태라는 판단에 있어서는 담당 의사와 감정 의무의 견해가 다를 수 있기 때문이다.

둘째, 대법원 판결은 진료를 거부하거나 진료중단을 요구할 수 있는 환자의 소극적 자기결정권 행사와 국가의 생명보호의무와의 관계를 폭넓게 규명하지 않고 문제의 범위를 한정하여 있다는 점이다. 진료의 시작 방법을 선택할 수 있는 적극적 자기결정권과 진료거부나 중단을 요구할 수 있는 소극적 자기결정권은 구분해야 한다. 그러나 이는 진료거부나 중단을 요구할 수 있는 소극적 자기결정권을 구분해야 한다. 그 근거와 관련하여 전자는 인간의 존엄성을 보장하므로 동일한 형식으로도 보장하지 않고 후자는 전문가의 의견을 배척할 수 있는 형식으로 보장된다. 그러므로 대법원은 진료거부나 중단을 요구할 수 있는 소극적 자기결정권을 구분해야 한다. 그 근거와 관련하여 전자는 인간의 존엄성을 보장하므로 동일한 형식으로도 보장하지 않고 후자는 전문가의 의견을 배척할 수 있는 형식으로 보장된다. 그러므로 대법원은 진료거부나 중단을 요구할 수 있는 소극적 자기결정권을 구분해야 한다. 그 근거와 관련하여 전자는 인간의 존엄성을 보장하므로 동일한 형식으로도 보장하지 않고 후자는 전문가의 의견을 배척할 수 있는 형식으로 보장된다. 그러므로 대법원은 진료거부나 중단을 요구할 수 있는 소극적 자기결정권을 구분해야 한다. 그 근거와 관련하여 전자는 인간의 존엄성을 보장하므로 동일한 형식으로도 보장하지 않고 후자는 전문가의 의견을 배척할 수 있는 형식으로 보장된다. 그러므로 대법원은 진료거부나 중단을 요구할 수 있는 소극적 자기결정권을 구분해야 한다. 그 근거와 관련하여 전자는 인간의 존엄성을 보장하므로 동일한 형식으로도 보장하지 않고 후자는 전문가의 의견을 배척할 수 있는 형식으로 보장된다. 그러므로 대법원은 진료거부나 중단을 요구할 수 있는 소극적 자기결정권을 구분해야 한다. 그 근거와 관련하여 전자는 인간의 존엄성을 보장하므로 동일한 형식으로도 보장하지 않고 후자는 전문가의 의견을 배척할 수 있는 형식으로 보장된다. 그러므로 대법원은 진료거부나 중단을 요구할 수 있는 소극적 자기결정권을 구분해야 한다. 그 근거와 관련하여 전자는 인간의 존엄성을 보장하므로 동일한 형식으로도 보장하지 않고 후자는 전문가의 의견을 배척할 수 있는 형식으로 보장된다. 그러므로 대법원은 진료거부나 중단을 요구할 수 있는 소극적 자기결정권을 구분해야 한다. 그 근거와 관련하여 전자는 인간의 존엄성을 보장하므로 동일한 형식으로도 보장하지 않고 후자는 전문가의 의견을 배척할 수 있는 형식으로 보장된다. 그러므로 대법원은 진료거부나 중단을 요구할 수 있는 소극적 자기결정권을 구분해야 한다. 그 근거와 관련하여 전자는 인간의 존엄성을 보장하므로 동일한 형식으로도 보장하지 않고 후자는 전문가의 의견을 배척할 수 있는 형식으로 보장된다. 그러나 의료기준에 의하여 진료를 거부하거나 진료중단을 요구할 수 있는 환자의 소극적 자기결정권 행사와 국가의 생명보호의무와의 관계를 폭넓게 규명하지 않고 문제가의 범위를 한정하여 있다는 점이다. 진료의 시작 방법을 선택할 수 있는 적극적 자기결정권과 진료거부나 중단을 요구할 수 있는 소극적 자기결정권은 구분해야 한다. 그 근거와 관련하여 전자는 인간의 존엄성에서 도출되지만 후자는 전문가의 의견으로서 도출된다. 그러나 진료거부나 중단을 요구할 수 있는 소극적 자기결정권은 구분해야 한다. 그 근거와 관련하여 전자는 인간의 존엄성에서 도출되지만 후자는 전문가의 의견으로서 도출된다. 그러나 진료거부나 중단을 요구할 수 있는 소극적 자기결정권은 구분해야 한다. 그 근거와 관련하여 전자는 인간의 존엄성에서 도출되지만 후자는 전문가의 의견으로서 도출된다. 그러나 진료거부나 중단을 요구할 수 있는 소극적 자기결정권은 구분해야 한다. 그 근거와 관련하여 전자는 인간의 존엄성에서 도출되지만 후자는 전문가의 의견으로서 도출된다. 그러나 진료거부나 중단을 요구할 수 있는 소극적 자기결정권은 구분해야 한다. 그 근거와 관련하여 전자는 인간의 존엄성에서 도출되지만 후자는 전문가의 의견으로서 도출된다. 그러나 진료거부나 중단을 요구할 수 있는 소극적 자기결정권은 구분해야 한다. 그 근거와 관련하여 전자는 인간의 존엄성에서 도출되지만 후자는 전문가의 의견으로서 도출된다. 그러나 진료거부나 중단을 요구할 수 있는 소극적 자기결정권은 구분해야 한다. 그 근거와 관련하여 전자는 인간의 존엄성에서 도출되지만 후자는 전문가의 의견으로서 도출된다. 그러나 진료거부나 중단을 요구할 수 있는 소극적 자기결정권은 구분해야 한다. 그 근거와 관련하여 전자는 인간의 존엄성에서 도출되지만 후자는 전문가의 의견으로서 도출된다. 그러나 진료거부나 중단을 요구할 수 있는 소극적 자기결정권은 구분해야 한다. 그 근거와 관련하여 전자는 인간의 존엄성에서 도출되지만 후자는 전문가의 의견으로서 도출된다. 그러나 진료거부나 중단을 요구할 수 있는 소극적 자기결정권은 구분해야 한다. 그 근거와 관련하여 전자는 인간의 존엄성에서 도출되지만 후자는 전문가의 의견으로서 도출된다. 그러나 진료거부나 중단을 요구할 수 있는 소극적 자기결정권은 구분해야 한다. 그 근거와 관련하여 전자는 인간의 존엄성에서 도출되지만 후자는 전문가의 의견으로서 도출된다. 그러나 진료거부나 중단을 요구할 수 있는 소극적 자기결정권은 구분해야 한다. 그 근거와 관련하여 전자는 인간의 존엄성에서 도출되지만 후자는 전문가의 의견으로서 도출된다. 그러나 진료거부나 중단을 요구할 수 있는 소극적 자기결정권은 구분해야 한다. 그 근거와 관련하여 전자는 인간의 존엄성에서 도출되지만 후자는 전문가의 의견으로서 도출된다. 그러나 진료거부나 중단을 요구할 수 있는 소극적 자기결정권은 구분해야 한다. 그 근거와 관련하여 전자는 인간의 존엄성에서 도출되지만 후자는 전문가의 의견으로서 도출된다. 그러나 진료거부나 중단을 요구할 수 있는 소극적 자기결정권은 구분해야 한다. 그 근거와 관련하여 전자는 인간의 존엄성에서 도출되지만 후자는 전문가의 의견으로서 도출된다. 그러나 진료거부나 중단을 요구할 수 있는 소극적 자기결정권은 구분해야 한다. 그 근거와 관련하여 전자는 인간의 존엄성에서 도출되지만 후자는 전문가의 의견으로서 도출된다.
타당하다면 의사의 진료를 중단해야 하는가 혹은 중단할 수 있는가, 대법원의 판결은 문제의 범위를 한정하여 이러한 의문에 대한 답변을 회피하고 있다. 예를 들어, 사전의료지시서의 정의 자체를 '회복불가능한 사망단계에 이르렀음' 경우에 대비하여 미리 의사의 말을 받아야 한다고 하였다. 이런 대법원의 판결이 환자의 소극적 자기결정권 행사와 의사에 대한 진료강제를 통해 나타나는 국가의 생명보호의무의 관계를 폭넓게 규명하지 않은 것은 아쉬움으로 남는다.

한편, 환자의 소극적 자기결정권과 국가의 생명보호의무의 관계는 치료중단의 두 가지 핵심적 요건(환자의 상태와 환자의 소극적 자기결정권 상호간의 문제로 해결됨)을 확보하였다. 일반적으로, 환자의 소극적 자기결정권의 성립으로 보고되는 것이나 체면히 문제의 범위를 한정하여 이러한 의문에 대한 답변을 회피하고 있다. 예를 들어, 사전의료지시서의 정의 자체를 '회복불가능한 사망단계에 이르렀을 경우'에 대비하여 미리 의사의 말을 받아야 한다고 함 것이다. 만약 환자의 소극적 자기결정권이 국가의 생명보호의무 등에 의하여 제한된다면, 그 제한의 의사에 대한 진료를 통하여 실현된다는 점에서 그만큼 더 환자의 상태를 엄밀하게 정의하려는 경향이 있을 것이다. 미국의 연명치료 중단 관련 법들이 대체로 환자의 '발기 상태'에 관하여 엄밀한, 세세한 정의를 하지 않고 있는 배경에는 환자의 소극적 자기결정권은 의학적인 판단에서 비합리적일지라도 보호되어야 한다는 서구 사회의 일반적 관념이 깊게 깔려 있는 것으로 생각한다.

셋째, 대법원 판결은 연명치료 중단의 일반적 범위를 구성함에 있어 그 일반 당사자인 의사를 무 수동적이며 기계적인 존재로 파악하고 있다. 의사의 환자에게 의학적으로 타당한 진료를 해야 한다는 의료계약의 본질상 당연한 것이며 의료법, 국민건강보험법 등에 의한 의무에서 방해를 받는 의무자와 간극의 의사의 의학적 범위를 구체화하려 하기 위해서는 의사의 의학적 범위에 대한 정의가 없으면 되는 경향이 있다. 이 경우 의사의 의학적 범위가 정의되지 않으면서 의료법상 의무를 해야 한다고 할 수 있는 구체적인 의무는 의사의 의학적 범위에 대한 정의가 없을 경우에는 의사의 의학적 범위의 문제를 제기를 할 수 없는 경향에 있다. 이론적 관점에서도 의사의 의학적 범위가 정의되지 않으면서 의료법상 의무를 해야 한다고 할 수 없는 경향에 있다. 이 경우 의학적 범위에 대한 정의가 없으면서 의료법상 의무를 해야 한다고 할 수 없는 경향에 있다. 이 경우 의학적 범위에 대한 정의가 없을 경우에는 의사의 의학적 범위의 문제를 제기를 할 수 없는 경향에 있다. 이론적 관점에서도 의사의 의학적 범위가 정의되지 않으면서 의료법상 의무를 해야 한다고 할 수 없는 경향에 있다. 이 경우 의학적 범위에 대한 정의가 없을 경우에는 의사의 의학적 범위의 문제를 제기를 할 수 없는 경향에 있다. 이론적 관점에서도 의사의 의학적 범위가 정의되지 않으면서 의료법상 의무를 해야 한다고 할 수 없는 경향에 있다. 이 경우 의학적 범위에 대한 정의가 없을 경우에는 의사의 의학적 범위의 문제를 제기를 할 수 없는 경향에 있다. 이론적 관점에서도 의사의 의학적 범위가 정의되지 않으면서 의료법상 의무를 해야 한다고 할 수 없는 경향에 있다. 이 경우 의학적 범위에 대한 정의가 없을 경우에는 의사의 의학적 범위의 문제를 제기를 할 수 없는 경향에 있다. 이론적 관점에서도 의사의 의학적 범위가 정의되지 않으면서 의료법상 의무를 해야 한다고 할 수 없는 경향에 있다. 이 경우 의학적 범위에 대한 정의가 없을 경우에는 의사의 의학적 범위의 문제를 제기를 할 수 없는 경향에 있다. 이론적 관점에서도 의사의 의학적 범위가 정의되지 않으면서 의료법상 의무를 해야 한다고 할 수 없는 경향에 있다. 이 경우 의학적 범위에 대한 정의가 없을 경우에는 의사의 의학적 범위의 문제를 제기를 할 수 없는 경향에 있다. 이론적 관점에서도 의사의 의학적 범위가 정의되지 않으면서 의료법상 의무를 해야 한다고 할 수 없는 경향에 있다. 이 경우 의학적 범위에 대한 정의가 없을 경우에는 의사의 의학적 범위의 문제를 제기를 할 수 없는 경향에 있다. 이론적 관점에서도 의사의 의학적 범위가 정의되지 않으면서 의료법상 의무를 해야 한다고 할 수 없는 경향에 있다. 이 경우 의학적 범위에 대한 정의가 없을 경우에는 의사의 의학적 범위의 문제를 제기를 할 수 없는 경향에 있다. 이론적 관점에서도 의사의 의학적 범위가 정의되지 않으면서 의료법상 의무를 해야 한다고 할 수 없는 경향에 있다. 이 경우 의학적 범위에 대한 정의가 없을 경우에는 의사의 의학적 범위의 문제를 제기를 할 수 없는 경향에 있다. 이론적 관점에서도 의사의 의학적 범위가 정의되지 않으면서 의료법상 의무를 해야 한다고 할 수 없는 경향에 있다. 이 경우 의학적 범위에 대한 정의가 없을 경우에는 의사의 의학적 범위의 문제를 제기를 할 수 없는 경향에 있다. 이론적 관점에서도 의사의 의학적 범위가 정의되지 않으면서 의료법상 의무를 해야 한다고 할 수 없는 경향에 있다. 이 경우 의학적 범위에 대한 정의가 없을 경우에는 의사의 의학적 범위의 문제를 제기를 할 수 없는 경향에 있다. 이론적 관점에서도 의사의 의학적 범위가 정의되지 않으면서 의료법상 의무를 해야 한다고 할 수 없는 경향에 있다. 이 경우 의학적 범위에 대한 정의가 없을 경우에는 의사의 의학적 범위의 문제를 제기를 할 수 없는 경향에 있다. 이론적 관점에서도 의사의 의학적 범위가 정의되지 않으면서 의료법상 의무를 해야 한다고 할 수 없는 경향에 있다. 이 경우 의학적 범위에 대한 정의가 없을 경우에는 의사의 의학적 범위의 문제를 제기를 할 수 없는 경향에 있다. 이론적 관점에서도 의사의 의학적 범위가 정의되지 않으면서 의료법상 의무를 해야 한다고 할 수 없는 경향에 있다. 이 경우 의학적 범위에 대한 정의가 없을 경우에는 의사의 의학적 범위의 문제를 제기를 할 수 없는 경향에 있다. 이론적 관점에서도 의사의 의학적 범위가 정의되지 않으면서 의료법상 의무를 해야 한다고 할 수 없는 경향에 있다. 이 경우 의학적 범위에 대한 정의가 없을 경우에는 의사의 의학적 범위의 문제를 제기를 할 수 없는 경향에 있다. 이론적 관점에서도 의사의 의학적 범위가 정의되지 않으면서 의료법상 의무를 해야 한다고 할 수 없는 경향에 있다. 이 경우 의학적 범위에 대한 정의가 없을 경우에는 의사의 의학적 범위의 문제를 제기를 할 수 없는 경향에 있다. 이론적 관점에서도 의사의 의학적 범위가 정의되지 않으면서 의료법상 의무를 해야 한다고 할 수 없는 경향에 있다. 이 경우 의학적 범위에 대한 정의가 없을 경우에는 의사의 의학적 범위의 문제를 제기를 할 수 없는 경향에 있다. 이론적 관점에서도 의사의 의학적 범위가 정의되지 않으면서 의료법상 의무를 해야 한다고 할 수 없는 경향에 있다. 이 경우 의학적 범위에 대한 정의가 없을 경우에는 의사의 의학적 범위의 문제를 제기를 할 수 없는 경향에 있다. 이론적 관점에도
참 고 문 헌

10. Malette v Shulman (1990), 37 OAC 281 (CA).
연명치료 중지 지침과 말기 암 환자 관리에 관한 윤리적 고찰
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연명치료 중지에 관한 지침의 대강

1. 연명치료 중지 결정의 원칙

- 회복 가능성이 없는 환자 본인의 결정과 의사의 의학적 판단에 의하여 ‘무의미한’ 연명치료를 중지(시행하지 않음을 포함한다. 이하 같다.)할 수 있다.
- 환자는 담당의사로부터 자신의 상병에 대한 적절한 정보와 설명을 듣고 협의를 통하여 스스로 결정하여야 하고, 그 결정은 존중되어야 한다.
- 담당의사는 연명치료의 적용 여부와 범위, 의료 내용의 변경 등을 환자와 그 가족에게 설명하고 협의하여야 하고, 연명치료에 관한 의학적 판단은 반드시 다른 전문의사 또는 병원윤리위원회에 자문하여야 한다.
- 담당 의료진은 통증이나 다른 불편한 증상을 충분히 완화하며, 환자나 가족의 정신적, 사회경제적적 도움을 포함한 종합적인 의료를 실시하거나, 대안으로 완화의료를 권유한다.
- 의도적으로 생명을 단축하거나 환자의 자살을 돕는 행위는 허용하지 않는다.

2. 연명치료 중지의 대상

1) 연명치료를 적용해야 하는 대상은 2명 이상의 의사가 회복 가능성이 없다고 판단한 말기 환자 또는 지속적 식물상태(PVS: persistent vegetative state)의 환자이다.

- 말기 환자란 원인 상병이 중증이고 회복할 수 없는 환자이다. 말기 환자에 대한 의료는 주로 대증적(對症的)이 연명치료이며, 원인에 대한 치료는 현재의 의료 수준에 비추어 불가능하거나 그 효과가 미약하다.

- 지속적 식물상태는 심한 뇌 손상으로 지각(知覺) 능력이 완전히 소실되어 외부 자극에 대하여 의미 있는 반응이 없는 상태가 지속되는 경우를 말한다.

연명치료 중지의 대상 환자는 다음과 같다.

① 말기 암 환자: 수술, 방사선 치료, 항암 화학요법 등의 적극적인 치료가 효과가 없거나 미약한 경우

② 말기 후천성면역결핍중 환자: 인간면역결핍바이러스에 감염된 뒤에 치명적인 감염중 등이 발생하여 적극적인 치료에 반응이 없거나 미약한 경우

③ 만성 질환의 말기 상태 환자: 심장·뇌·간·신장·근육 등의 만성 질환이나 진행성 질환의 말기 상태로 치료 방법이 없거나 효과가 미약한 경우

④ 뇌사 상태 환자: 법률에 정의된 뇌사로 진단되었거나 뇌사 판정 기준 가운데 무호흡 검사 등 일부 기준은 제외한 나머지 기준이 충족되어 2인 이상의 전문의사가 이에 준한다고 판정한 경우.

⑤ 임종 환자: 말기 환자 가운데 상태가 극히 위중하여 여러 계통의 기능이 매우 저하되거나 심한 상태(multi-organ failure)이며, 적극적인 치료를 하여도 죽음이 임박하여 짧은 시간에 사망할 것으로 예상되는 경우.
지속적 식물상태 환자: 식물상태로 6개월 이상이 지났고 회복 가능성 없는 경우.

2) 임종 환자: 말기환자 가운데 상태가 극히 위중하여 여러 계통의 기능이 매우 저하되었거나 상실된 상태(multi-organ failure)여서, 적극적인 치료를 하여도 죽음이 임박하여 짧은 시간에 사망할 것으로 예상되는 경우.

3. 중지되는 연명치료

1) 일반 연명치료는 생명유지에 필수적이지만 전문적인 의학적 지식이나 의료 기술, 특수한 장치가 필요하지 않은 치료로 예를 들어 관(drip)을 통한 영양과 수분과 산소 공급, 제온 유지, 배변과 복부 도움, 진통제 투여, 욕창 예방, 일차 환생제 투여 등이다.

특수 연명치료는 생명유지에 필수적이며 고도의 전문적인 의학적 지식과 의료 기술, 특수한 장치가 필요하며 환자에게 고온을 초래할 수 있는 심폐소생술, 인공호흡기 적용, 혈액투석, 수혈, 장기이식, 항암제 투여, 가토하 투여 등이다. 심폐소생술은 심장마사지, 심장세동기(除細動器, defibrillator) 적용, 인공호흡기를 포함한다.

2) 제1 단계: 임종 환자 또는 뇌사 상태 환자: 임종환자는 의학적 판단과 가족의 동의에 따라 연명치료를 중지할 수 있다. 뇌사가 있는 경우는 의학적 판단에 따라 연명치료를 중지할 수 있다.

제2 단계: 의사결정 능력이 없으며 특수 연명치료를 적용해야 할 환자가 특수 연명치료를 적용하고 있거나 적용해야만 생존할 수 있는 상태라면,

(1) 환자의 구체적이고 명시적인 의사 표시를 존중한다.

(2) 만약 환자의 동의가 없거나 명시적이며 의도적으로 의사 표시를 하지 않는 경우, 성인이 추정적 의사로서, 의학적 판단을 하여야 한다. 

병원윤리위원회는 담당의사 이외에 2명 이상의 전문의사가 환자의 의학적 판단을 판단하도록 하며, 환자의 추정적 의사표시는 포괄적인 사전의료지시, 환자의 신명, 평소의 의사의 진단 등에 기초한다.

병원윤리위원회는 위의 사항 이외에 가족들의 동의, 이미 지출되었거나 앞으로 지출할 비용, 환자와 가족의 상황과 상태에 따라 같은 절차로 중지할 수 있다.

병원윤리위원회는 당해 의료기관에서 연명치료 중지 여부뿐 아니라 다른 의료기관으로 전원(轉院) 여부도 결정할 수 있다.

3) 심폐소생술과 인공호흡기는 시행하지 않거나 중지할 수 있으며, 다른 특수 연명치료는 환자와 가족의 동의 및 상태에 따라 같은 절차로 중지할 수 있다.

연명치료 중지에 관한 윤리적 해석

1. 연명치료 중지 결정의 원칙에서 - “의도적으로 생명을 단축하거나 환자의 자살을 돕는 행위는 허용하지 않는다.”의 의미는 무엇인가?

자연과학적 행위 개념은 "인간 외부에 일어나는 거동에 의하여 외부의 변화가 나타나는 것이 다." 하지만 법적으로 의미있는 행위는, 행위자가 자신의 거동에 대하여 가지는 의사 내용을 고려하여야 한다. 이러한 행위자가 가지는 내면적인 행위의 의미는 행위에 대한 가치 판단을 가능하게

1) 가족의 동의는 원칙적으로 배우자, 부모, 정신인 적계존비속이 합의함으로써 성립하지만, 가족이 합의할 수 없을 때에는 근친 중에서 관할하는 배우자, 부모, 자식의 연장자 순서에서 최우선 순위자 1인의 서면 동의로써 성립한다. 가족이 있을 때에는 후견인 또는 보호자가 대신한다.

2) 예를 들어 상황을 작성한 사전의료지시서나 생전유서
환자 생명에 대한 연명 치료 중지에서 의도적으로 생명을 단축하지 않겠다는 것은 연명 중지 행위를 할 때, 그 결정을 한 의도가 환자의 죽음이어야 한다는 것이다. 이러한 접근은 일반적으로 말기 환자에 대한 연명 치료 중지에 커다란 해석의 여지를 던져 주고 있는데, 이번 지침은 이 문제가 대하여 연명치료를 일반 연명치료와 특수 연명치료로 구분함으로써 객관적인 기준에 의하여 답을 주고 있다.

 먼저 일반 치료로서, 급식관의 제거는 반드시 환자의 죽음을 초래한다. 그러므로 급식관을 제거하는 행위는 죽음을 의도한 행위가 된다. 그러므로 지침에 의하면 병원에서 이 문제를 결정할 수 없다.

둘째, 특수 연명 치료로서 인공호흡기의 제거는 급식관의 제거와 달리 환자의 사망에 대한 확신은 없는 상황이다. 이 치료는 일반적으로 중환자실에서 이루어지는 것으로서, 인공호흡기를 제거할 경우 환자가 사망할지에 대하여는 아직은 확신이 없고 한편으로 말기 암 환자에 대하여 인공호흡기를 제거하여도 어색하며 사망하지 않고 자발 호흡을 유지할 수도 있다는 의식은 의료진이 가지고 된다. 그러므로 이러한 경우에 인공호흡기의 제거는 가능한 환자의 자발 호흡을 유지하기를 원한다는 선언도 가지고 행하는 것으로 해석될 수 있다. 이러한 접근법은 기독교 윤리 이론에서 유래한 이중효과(Double effect)에 의하여도 정당화 된다.

 일반 연명치료와 특수 치료를 구분한 기준은 다음과 같다.

 일반 연명치료는 생명유지에 필수적이지만 전문적인 의학적 지식이나 의료 기술, 특수한 장치가 필요하지 않은 치료이다. 관(管)을 이용한 영양 공급, 수분·산소 공급, 체온 유지, 배변과 배뇨 도움, 진통제 투여, 유방 예방, 일차 항생제 투여 등이 있다.

 지침에서는 일반 연명치료를 하나의 범주로 구분하면서 병원의 일반 병실 또는 가정에서 가능한 치료의 종류를 열거하고 있다. 이러한 연명치료를 중지하는 것은 빠르고 그것이 급식관의 제거와 같 이 측각적으로 명백하게 죽음을 초래하지 않더라도, 그것은 행위자가 환자의 죽음을 의도하는 것이 라고 판단하여야 한다는 강한 추정을 인정하는 것이다.

 이러한 설명은 특수연명 치료에 대한 설명에도 적용된다. 하지만 특수 연명치료로서 인공호흡기의 제거가 반드시 환자의 죽음을 의도하는 경우는 없을까?

 만약 말기 암환자가 치료 중에 뇌출혈이 발생하였고, 뇌성태에 빠졌을 경우에, 인공호흡기를 제거한다면, 환자가 죽을 것이라는 "의도"가 있다고 평가 할 수 있다. 일반적으로 말기 환자 중에서 죽음 임박한 입종환자나 뇌성태(상태)의 환자는 말기 환자와는 다른 부류의 상태로 본다.

 우리는 이 지점을 통하여 측각적인 죽음을 초래할 수 있는 인공호흡기의 제거를 인정할 수 있는가? 지침은 이 부분은 일반적인 연명치료 중지의 대상으로 몰아 놨았기 때문에, 죽음이 의도된 인공호흡기 중단이 어려워지는 이론적 모순에 처하게 된다. 말기 환자와 구분하여 다른 법적으로 분류하여야 할 것이다.

연명 치료의 중지

연명치료에 대한 일반적인 구분은 치료의 보류(withhold)와 치료의 철회(withdraw)로 구분된다. 이러한 구분에 대한 많은 철학적 논의는 논외로 하고, 위 지침은 이 두 가지 행위에 규범적 차이를 인정하지 않았다. 1970년 카렌 퀸란 사건 당시에는 미국의사협회는 치료 보류와 치료 철회는 다르게 보았다. 치료 보류는 허용되지만, 이미 치료를 시작한 경우에 치료 철회는 허용되지 않는다는 입장이었다. 하지만 이후 사회적 논쟁이 진행하면서, 의료 현장에서 치료를 보류하는 것과 철회하는 것
사이에 차이는 없는 것으로 의사윤리규정을 개정하게 된다.

연명치료의 중지의 근거는 환자의 명시적 또는 추정적 의사(意)를 기준으로 하였다. 환자가 가지는 자기 결정권을 기준으로 했는데, 이것은 의학의 의미에서도 상황이 있다고 판단되는 경우, 환 자 또는 환자 가족이 연명치료를 계속해 줄 것을 요청하는 경우에는 이러한 진료 요청을 거부할 수 있는 지에 대하여 규정하지 않고 있다. 유아가 환자의 명시적 의사 또는 추정적 의사에 의하여 연명치료가 중지된 경우, 환자 상태가 나빠지면서 환자 가족이 연명 치료를 다시 계속해 줄 것을 요구한다면, 어떻게 할 것인가?

무의미한 치료라는 것은 결국은 환자 측이 요구하거나 거절하더라도 더 이상 진행될 근거가 없는 과학적 근거를 의미한다. 무의미한 연명 치료 중지에 대한 논의는 의사의 진료 거부권인정 문제로 번지나갈 수 밖에 없고, 이에 반대하는 우리의 목소리도 높다.

하지만 이번 지침안에는 의료의 무의미성이 인정되는 경우에도 환자의 명시적 또는 추정적 의사에 기하여 연명 치료를 중지하는 것으로 규정하였다. 그러므로 환자 측이 연명 치료 중지를 요청하는 경우에는 이 지침이 적용되지만, 환자 또는 환자 측이 연명 치료를 계속해 줄 것을 요구하는 경우에는 비록 그 의료가 무의미하다고 하더라도 그 요구를 거절할 수는 없다. 유아가 환자가 연명치료를 중지해달라는 요구를 했다가 다시 마음을 바꾸어 연명 치료를 재개하도록 요구한다면 역시 그러한 요구를 거절한 근거는 없다고 보아야 한다.

병원윤리위원회

연명치료 중지에 대한 절차적 정당성을 확보하는 가장 중요한 요소로 나타난 것이다. 의료진은 죽음을 결정하는 과정에 최대한 선한 의지를 보여야 하고, 그러한 의지는 절차적으로 다수의 지혜를 모으는 과정을 통하여 확보하는 것이 다. 다만 병원윤리위원회가 어떻게 구성되어야 하는 가에 대한 규정, 병원윤리위원회의 결정에 근거 규정은 없다. 그러므로 병원윤리위원회의 구성과 결정은 의학적인 것이다.

하지만 연명 치료 중지다는 결정은 과학적 의학적 우려가 있음을 생각한다면, 위원회 구성에 대하여 신중하게 고려할 필요가 있다.

첫째는 위원회 구성에 비의료인과 해당 의료기관외에 종사하는 자가 반드시 참여하여야 한다. 그러한 구성의 다양성을 통하여 죽음에 대한 결정이 의료진 내부에서 배타적으로 이루어지는 것이 아니라, 사회의 참여를 허용하고 이를 죽음의 문제를 하나로 인정하는 것이 필요하다.

둘째는 병원윤리위원회의 결정에 대한 실질적인 효력을 어떠한 결정이 여려으며, 이론적으로는 주체의가 병원윤리위원회의 결정을 거부하는 것도 가능하다. 하지만 이러한 일은 발생하기 어려울 것으로 본다. 반대로 법률에 의하여 위원회 결정의 효력을 강제하는 것이 필요할지라도 의문은 없다. 지금은 병원윤리위원회에 대하여 자율적인 규칙을 설정하는 과정이며, 전달한 운용을 통하여 사회적 신뢰를 얻어가는 과정이라는 것이다.

임종 환자와 뇌사 상태 환자의 의미

이번 지침은 임종 환자/뇌사상태 환자와 말기 환자/지속적 식물 상태 환자를 구분하여 두 가지 카테고리로 분류하고 있다. 임종 환자에 대한 hopeless discharge는 의료 실무상 지금까지 문제없이 진행되었던 것인데, 이번 지침은 이것을 명시적으로 인정하였다. 다만 실무적으로 말기 환자와 임

3) 이 문제는 미국의 텍사주 주법에 의하여 인정되는 환자 강제 퇴원에 대한 법률 규정을 보면 잘 알 수 있다 이에 대하여는 헌고 조영사에 대한 미국의학회 대한의료보고 헌고 법학. 9권 2호, 53면. 2008. 참조.
종 환자의 구분이 명확하지 않아서 논란의 여지가 있다. 말기 환자의 일반 치료 중지는 법원이 결정하도록 하고 있지만, 임종 환자의 일반치료는병원이 결정하도록 하기 때문에, 말기 환자를 임종 환자로 잘못 인정하는 경우, 이 점에서 인정하지 않은 방식으로 일반 연명치료가 중지될 수가 있다.

현실적으로 이 문제를 해결하는 방법은 병원윤리위원회가 정확하게 일을 수행하는 것이 될 것이 다. 정부로서는 병원윤리위원회의 운영에 대한 감시를 통하여 이 문제를 사후적으로 감시하게 될 것이다. 이러한 절차적 통제 외에 의도적으로 판정을 왜곡할 경우에 사후적인 처벌 역시 가능할 것이다.

뇌사 상태 환자는 무호흡 검사를 제외한 다른 뇌사 판정 기준을 만족하는 경우에 임종환자와 동일하게 퇴원을 가능하게 하였다. 뇌사 판정 기준, 특히 무호흡 검사가 뇌사 판정에 가장 어려울 부분이라는 학계의 기존 주장은 인정한 것이다. 다만 이러한 뇌사 상태 환자의 장기를 채취하여 장기 이식하는 것은 장기이식법에 관한 법률을 우회하는 것이므로 어려울 것으로 판단한다.
Oral Presentation

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Background: There is a paucity of literature describing the willingness to pay (WTP) for treatments in cancer patients within Korea. This research is designed to evaluate the WTP for anti-cancer treatments in metastatic breast cancer patients. Methods: This is a multicenter, cross-sectional study in breast cancer patients receiving palliative chemotherapy. Clinical, socio-demographic, and quality of life data were collected. Subjects then completed a face-to-face interview with trained interviewer to assess their willingness to pay for breast cancer treatment. WTP values were summarized and evaluated for subject characteristic differences to better understand the influence of age, income, family history, clinical staging, etc. Results: Total 200 patients with metastatic breast cancer were interviewed from 4 centers. Seventy nine percent of patients were married with mean age of 49.3 years, and 68% have additional health insurances. 127 patients (63.5%) underwent mastectomy in the past. 102 patients (51%) had additional health insurances. 127 patients (63.5%) underwent mastectomy in the past. 102 patients (51%) had metastatic disease with bone metastasis. ECOG performance status was 0 (22%) and 1 (71%). Average monthly WTP for treatment was W13,274,550. Education, income and other insurance didn’t have influence on WTP values. WTP values ranged from W0-100 million. WTP values did not significantly differ by center or starting bid. Conclusion: Korean breast cancer patients WTP for anti-cancer treatment was not affected by center, education, income, or insurance. WTP is an important component in understanding the inherent value of treatment as perceived by the patient. When combined with improvements in quality of life, the results of cost-effectiveness studies can be put into the patient’s perspective.

Keywords: Metastatic, Breast cancer, Willingness to pay

Who Can Have Benefit from Intensified Surveillance Program in Postoperative Breast Cancer Patients?

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Background: Despite improvement in surgical management and strides in systemic treatment, metastatic breast cancer remains an incurable condition for the majority of patients. Early detection and aggressive treatment of tumor recurrence provide the best chance for long-term survival even in patients with effective adjuvant treatments were performed. Earliest possible institution of systemic therapy in the presence of minimal tumor burden and good performance status may also possess a greater likelihood of response and therefore the most favorable outcomes. The purpose of the study is to evaluate the need of intensified surveillance program after breast cancer surgery in terms of suggested proper time-interval and imaging techniques. In addition, we are to evaluate who can be candidate patients at greater risk for relapse. Methods: We retrospectively analyzed the clinicopathologic characteristics and outcomes of patients with invasive breast cancer who received definitive surgery from 2000 to 2004 at Samsung Medical Center. Results: Among 1,881 patients who were received breast cancer surgery from 2000 to 2004, 361 patients (19.2%) showed relapse for median follow-up duration of 75 months. 259 patients were relapse at distant sites (71.7%). HER2 positivity (HR 2.3, p<0.0001), triple negativity (HR 1.6, p=0.007), high histologic grade (HR 1.6, p=0.001) and TNM stage 3 (HR 3.7, p<0.0001) were identified as independent risk factors to predict relapse. According to identified independent risk factors, risk stratification was performed. Classification among patients using the scores which is made with summation of the number of identified independent risk factors was conducted: score 0, no risk factor; score 1, 1 risk factor; score 2, 2 risk factors; score 3, 3 risk factors. The patients who have score 3 were identified as high-risk group of patients for relapse. This high-risk group was composed of two subsets of the patients: 1) the highest histologic grade and TNM stage 3 in HER2 overexpressing patients 2) the highest histologic grade and TNM stage 3 in TNBC patients. Median RFS of this high-risk group was 49 months. Most of the relapses were occurred within 2 years. Common metastatic sites were lymph nodes, bone, lung, and liver. 5-year survival rate of the high-risk patients was 65.0%. Conclusion: There is evidence for need of surveillance protocol in high-risk patients for relapses. Well designed prospective clinical study for intensified surveillance including proper imaging techniques for common metastatic sites after surgery is warranted.

Keywords: Surveillance, Breast cancer, High-risk

Clinical Features and Course of Brain Metastases in Triple Negative Breast Cancer: Comparison with HER2+ and Other Type

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Background: Incidences and clinical aggressiveness of intracranial metastasis in triple negative (TN) breast cancer have not been well delineated compared to HER2+ subtype. Methods: Patients (pts) who were diagnosed with primary breast cancer at Asan Medical Center from January 1990 to July 2006 were screened (Lee SS, Breast Cancer Res Treat 2008). All pts with brain metastases, identified by CT or MRI, were included and classified into three subtypes (TN, HER2+ and other). The clinical features and course of brain metastases with TN breast cancer, defined according to immunohistochemical staining and HER2 FISH analysis, were reanalyzed and compared among three groups. Results: Of 7,782 breast cancer pts, 198 pts developed brain metastases and 61 pts with unknown ER, PR or HER2 status were excluded. Of 137 pts, incidences of TN, HER2+ and other group were 32% (44), 50% (69) and 18% (24), respectively. The median age at the time of brain metastases was 46 years (yr)(range 29-70 yr) in TN group, 48 yr (range 27-78 yr) in HER2 group and 37 yr (range 25-62 yr) in other group with no significant difference. Clinical parameters such as performance status, previous adjuvant chemotherapy or radiotherapy, was similarly distributed among groups except that pts with earlier stages (I, II) were more prevalent in TN group compared to other two groups (59% vs 36% vs 38%, p<0.01). With a median follow-up duration of 99 months (m), the median time from initial diagnosis of primary breast cancer to brain metastases was significantly shorter in TN group, compared with other two groups [TN, HER2, other; 20 m vs 32 m vs 45 m, p<0.01] and the one from diagnosis of primary cancer to the first distant metastases at any sites was also shorter [16 m vs 23 m vs 23 m, p<0.005]. The median overall survival from diagnosis of primary cancer was significantly shorter in TN group [31 m vs 39 m vs 57 m, p=0.02] and however, the one after brain metastases was not different among 3 groups [5.9 m vs 5.2 m vs 8.8 m, p=0.31]. Conclusion: TN breast cancer showed earlier brain metastases, earlier distant metastases at any sites and shorter overall survival in spite of high proportion of early stages, compared with other phenotypes. Preventive and therapeutic strategies of brain metastases in TN breast cancer are urgently needed.

Keywords: Breast cancer, Metastasis, Triple-negative

The Prognostic Factors for the Recurrent Breast Cancer Patients with Isolated, Limited Number of Lung Metastases and the Implication of Pulmonary Metastasectomy

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Background: In recurrent breast cancer (BC) with isolated lung metastases, the role of pulmonary metastasectomy (PM) is not established. The aim of this study was to evaluate the clinical treatment outcomes of recurrent BC with a limited number of isolated lung metastases, and to evaluate the role of PM. Methods: We consecutively enrolled recurrent BC patients (pts) with isolated lung metastases from 1997 to 2007 in Seoul National University Hospital. Among 140 recurrent pts with isolated lung metastases, 45 pts had metastatic lesions less than 4. We analyzed the clinical treatment outcomes of these 45 pts. Results: The median age was 49.0 (range 32.0-67.0) years. The median disease-free interval (DFI: time from initial BC diagnosis to recurrence) was 26.1 (range 4.2-168.0) months, and the pts with DFI of less than 24 months were 20 (44%). The pts who had biologic subtypes (BS) of hormone receptor (HR)(+), HER2(+), triple negative (TN) were 16 (36%), 14 (31%) and 15 (33%), respectively. Fifteen (33%) had PM then followed by systemic treatment (PM group), and 30 received systemic treatment without PM (no PM group). There were no differences in terms of clinical factors such as DFI and BS between two groups. During a median follow-up duration of 50.1 months (range, 5.0-136.2 months), the median progression-free survival (PFS) and overall survival (OS) were 13.0 months (95% CI, 10.05-15.95) and 41.7 months (95% CI, 23.82-59.58), respectively. The median PFS and OS in the PM group were significantly longer than those in the non-PM group (PFS, not reached vs 10.1 months, p<0.001; OS, not reached vs 34.3 months, p=0.011). In univariate analysis for PFS, PFS was significantly longer in pts with PM (p<0.001), DFI of more than 24 months (p<0.001), and, was marginally significant according to BS (p=0.084). In multivariate analysis, DFI of less than 24 months (hazard ratio (HR), 4.53; 95% CI, 1.72-11.90), no PM (HR, 9.52; 95% CI, 3.34-27.18) and BS such as HER2(+) (HR, 3.00; 95% CI, 1.04-8.64) and TN (HR, 3.92; 95% CI, 1.32-11.59) were independent prognostic factors for shorter PFS. In univariate analysis for OS, OS was significantly longer in pts with PM (p=0.011), DFI of more than 24 months (p<0.001), HR (+)(p=0.009). In multivariate analysis, DFI of less than 24 months (HR, 7.67; 95% CI, 2.00-29.43) and BS such as HER2(+) (HR, 3.70; 95% CI, 1.03-13.24) and TN (HR, 3.27; 95% CI, 1.02-10.44) were independent prognostic factors for shorter OS. Conclusion: Our results show that DFI and biologic subtypes of the tumor are firm, independent prognostic factors for survival, and PM can be a reasonable treatment option in this population. Further prospective studies are warranted to evaluate the role of PM.

Keywords: Breast cancer, Lung metastasis, Prognostic factors, Pulmonary metastasectomy
The Clinical Outcome of Chemotherapy Induced Amenorrhea in Premenopausal Young Breast Cancer Patients with Long Term Follow Up

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Background: Adjuvant chemotherapy is known to prolong disease-free survival (DFS) and overall survival (OS) of breast cancer patients; however, the cytotoxicity of the chemotherapeutic drugs can induce premature menopause (amenorrhea). We investigated the factors predicting chemotherapy-induced amenorrhea (CIA) and the prognostic significance of CIA after long-term follow-up. Methods: We reviewed data from 241 premenopausal breast cancer patients who underwent adjuvant CMF (cyclophosphamide, methotrexate, fluorouracil) or FAC (fluorouracil, adriamycin, cyclophosphamide) chemotherapy after breast cancer surgery between January 1995 and December 2000. CIA was defined as cessation of menstruation for 6 months in patients who were premenopausal at diagnosis. Results: The median follow up duration was 109.8 months (range, 16.6-193.1 months). The median age of CIA patients was greater than that of non-CIA patients (44 years (range, 28-53) and 36 years (range, 25-49), respectively; p<0.001]. Addition of tamoxifen to the chemotherapy regimen increased the incidence of CIA from 48% to 63.6% (p=0.015). The 10-year DFS rate was higher in the CIA group than in the non-CIA group in hormone receptor-positive patients (78.4% vs. 67.0%, respectively, p=0.022), and the 10-year OS rate was also higher in the CIA group than in the non-CIA group (90.8% vs. 79.7%, respectively, p=0.041). However, there was no survival difference according to CIA in hormone receptor-negative patients. Furthermore, DFS and OS rate were significantly longer in the CIA group than in the non-CIA group for the subgroup with stage III disease. Conclusion: The most important predictors of CIA are age and addition of tamoxifen to the chemotherapy regimen. CIA appears to have an influence on DFS and OS in premenopausal breast cancer patients with hormone receptor-positive and advanced disease, and might be used as a predictive marker of effective chemotherapy in these young Asian patients. Keywords: Breast cancer, Amenorrhea, Premenopause, Adjuvant chemotherapy

Comparable Efficacies between Premenopausal and Postmenopausal Metastatic Breast Cancer Patients by Letrozole with and without Goserelin as First Line Hormone Therapy: A Phase II Parallel Group Study

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Background: The use of goserelin and letrozole in premenopausal patients, which induces effective estradiol (E2) suppression, would accomplish comparable clinical outcomes as in postmenopausal patients with metastatic breast cancer (MBC) by letrozole alone. Methods: Patients with hormone responsive metastatic breast cancer were included. Of those, 35 premenopausal patients received goserelin (3.6mg given subcutaneously every 28 days) plus letrozole (2.5mg per day given orally) and 38 postmenopausal patients received letrozole alone as their first line endocrine therapy in metastatic setting. Results: Baseline characteristics were similar in two groups except median age (41 years vs. 53.5 years, P<0.001) and median disease free interval (DFI) (1.8 years vs. 3.3 years, P=0.033). Serum estradiol level in premenopausal group was decreased to 8.4 ± 2.5 pg/mL at 4 weeks after the first goserelin injection. Clinical benefit rates were comparable between two groups (77.1% vs. 71.1%, P=0.770). With the median follow-up of 27.4 months, there was no statistical difference in median time to progression (TTP) between two groups (9.5 months [95% CI, 6.4-12.1 months] for premenopausal group vs. 8.9 months [95% CI, 6.4-13.3 months] in postmenopausal group). In patients who did not receive bisphosphonate, letrozole ± goserelin caused greater BMD loss at 6 months compared to that of patients receiving bisphosphonate treatment (premenopausal group, -16.7 % vs. 53.9%, P=0.002 at the lumbar spine, -20% vs. 8.3%, P=0.008 at the trochanter; postmenopausal group, -13.3% vs. 17.4%, P=0.037 at the lumbar spine, -33.5% vs. 10.5%, P=0.007 at the trochanter). Conclusion: Clinical efficacies in premenopausal MBC patients by combined letrozole and goserelin therapy were comparable to those in postmenopausal patients by letrozole alone. Although letrozole ± goserelin results in a modest increase in bone resorption in BMD, concurrent treatment with bisphosphonate could prevent bone loss during therapy and improved BMD at 6 months. Keywords: Letrozole, Goserelin, Breast cancer

DOS (Docetaxel, Oxaliplatin and S-1) Combination Chemotherapy in Metastatic Gastric Cancer: Results of a Phase II Study

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Background: Docetaxel, oxaliplatin and S-1 have shown significant single-agent efficacy in gastric cancer. These drugs have distinct mechanisms of action and no overlapped key toxicities. Furthermore, fluoropyrimidine and docetaxel or oxaliplatin have shown synergism in vivo studies and in clinical trials. We performed a phase II study of combination docetaxel, oxaliplatin and S-1 (DOS) to evaluate the efficacy and safety in metastatic gastric cancer. Methods: Eligible patients were those who had unresectable, locally advanced or metastatic, gastric adenocarcinoma. Both initially diagnosed and recurrent patients with no previous history of chemotherapy except adjuvant chemotherapy were enrolled. The patients of age 18 to 70 with ECOG PS 0-2 were enrolled to this study. Docetaxel 52.5 mg/m² and oxaliplatin 105 mg/m² were administered intravenously on day 1 and S-1 80 mg/m² was administered orally on days 1-14. Cycles were repeated every 21 days. Patients were treated until disease progression or unacceptable toxicity. Results: Forty-four patients (male/female 32/12; median age 55, range 25-69; ECOG PS 0/1/2 14/29/1) have been enrolled in this study. Ten patients had recurrent cancer after surgery and 34 patients were diagnosed as a metastatic disease. Tumor differentiation was 5 well, 12 moderate, and 27 poor. Main sites of metastasis were 37 lymph node, 19 peritoneum, 12 liver, 2 lung, 2 ovary, and 8 others. A total of 318 cycles were administered (median 8, range 1-29). Forty-two patients were evaluated for toxicity and forty for response. The common grade 3/4 toxicities were leukopenia (26% of patients), neutropenia (36%), febrile neutropenia (14%), anemia (12%), and deep vein thrombosis (12%). There were 2 CR and 22 PR. The overall response rate was 55% (95% CI, 40-70%) in intention to treatment. The preliminary median progression free survival was 7.9 (95% CI, 6.2-9.5) months and median survival time was 15.8 (95% CI, 6.5-25.1) months. Conclusion: These data suggest that DOS regimen is active and is well tolerated in patients with metastatic gastric cancer.

Keywords: Stomach cancer, Combination chemotherapy, Phase 2 trial

Bone Morphogenetic Protein-2 (BMP-2) Levels Are Elevated in Patients with Gastric Cancer and Correlate with Disease Progression

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Background: Bone Morphogenetic Proteins, members of the TGF-β superfamily, normally function to regulate embryonic development and cellular homeostasis as well, including regulation of proliferation, differentiation, and apoptosis. Bone morphogenetic protein-2 was reported to enhance migration, invasion, and metastasis at the various types of cancer cells. The purpose of this study is to identify the role of bone morphogenetic protein-2 in progression of gastric cancer. Methods: Fifty-four patients with operable gastric cancer were enrolled. Also ten healthy volunteers were enrolled as control group. All patients received gastrectomy with D2 lymphadenectomy and surgical staging was performed. Whole blood was obtained preoperatively in all patients and serum bone morphogenetic protein-2 levels were quantified by commercially available ELISA kit. Results: All patients showed increased serum bone morphogenetic protein-2 levels compared with control group, when upper normal limit was defined as the mean of control serum level + 2 x standard deviation. The mean serum bone morphogenetic protein-2 level of lymph node positive group was significantly elevated than that of lymph node negative group (382.7 pg/ml, 95% CI 341.99-423.4 pg/ml vs. 211.69 pg/ml, 95% CI 191.09-232.29 pg/ml, p<0.001). The serum bone morphogenetic protein-2 was strongly correlated with the depth of invasion (T stage) and the extent of regional lymph node involvement (N stage) (r=0.662, p<0.001 and r=0.831, p<0.001, respectively). Moreover, the serum bone morphogenetic protein-2 was correlated with the grade of tumor histology (r=0.421, p=0.008). The source of serum BMP-2 could be confirmed by Immunohistochemical stain for BMP-2 in gastric cancer tissue. Gastric cancer cells showed the positive immunohistochemical stain but normal tissues didn’t. Conclusion: In conclusion, serum bone morphogenetic protein-2 is associated with progression from early localized gastric cancer to locally advanced gastric cancer.

Keywords: Bone morphogenetic protein 2, Stomach neoplasm, Neoplasm invasiveness, Tumorigenesis, Enzyme-linked immunosorbent assay
Background: Stage IV gastric cancer (GC) in the 6th edition of American Joint Committee on Cancer (AJCC) staging system consists of heterogeneous prognostic subgroups. The purpose of this study was to evaluate the prognostic impact of subclassifying stage IV GC into IV(M0) and IV(M1) groups and to find prognostic factors in stage IV(M0) patients. Methods: Between Mar 2003 and May 2008, 2077 newly diagnosed gastric adenocarcinoma patients were identified. Among them, patients with stages IIIB and IV were included in this study. Stage IV cases were subclassified into Stage IV(M0; TxN0M0 or T4N1-2M0) and IV(M1; TxNxM1). Results: The stage distribution of patients was as follows: 57 stage IIIB, 116 stage IV(M0) and 361 stage IV(M1). The median age of all patients was 63 years (range, 21-89). The median overall survival (OS) was 39.4 months in stage IIIB, 25.1 months in stage IV(M0) and 8.7 months in stage IV(M1), respectively (P = 0.026 between stages IIIB and IV(M0); P < 0.001 between stages IV(M0) and IV(M1)). The median disease-free survival (DFS) after curative surgery was 22.4 months in stage IIIB and 11.7 months in stage IV(M0), respectively (P=0.016). In stage IV(M0) patients, the median retrieved lymph node (LN) number during the surgery procedure was 55 (range, 6-102). The ratio of tumor-positive LN numbers to all retrieved LN numbers (positive node ratio [PNR]) was median 36% (range, 2-95%). The N stage according to the AJCC staging system (6th edition) did not discriminate survival outcomes in stage IV(M0) patients. However, in a multivariate analysis, higher PNR (≥ 36%) was significantly associated with shorter DFS (Hazard ratio [HR], 3.19; 95% confidence interval [CI], 1.95-5.22; P < 0.001) compared with lower PNR (<36%). The N stage according to the AJCC staging system (6th edition) did not discriminate survival outcomes in stage IV(M0) patients. However, in a multivariate analysis, higher PNR (≥ 36%) was significantly associated with shorter DFS (Hazard ratio [HR], 3.19; 95% confidence interval [CI], 1.95-5.22; P < 0.001) compared with lower PNR (<36%). Conclusion: Stage IV(M0) GC shows significantly different survival outcomes compared with stages IIIB and IV(M1). Our study warrants that stage IV GC should be subclassified into IV(M0) and IV(M1) in the future GC staging system. PNR can discriminate prognostic subgroups in stage IV(M0) GC patients.

Keywords: Gastric cancer, Stage IV, Lymph node, Stage
Phase II Study of Fixed Dose-rate Infusion of Gemcitabine and UFT Combination Chemotherapy in Patients with Advanced Bile Duct Cancer: Daegu Gyeongbuk Oncology Group

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Background: This phase II study evaluated efficacy of fixed dose rate (FDR) infusion of gemcitabine (10 mg/m²/min) and UFT combination in chemo-naive patients with advanced bile duct cancer. Methods: This was an open-label, single-arm, multicenter, phase II study with a Simon two-stage minimax design. Patients received the FDR gemcitabine 1000 mg/m² for 3 consecutive weeks and UFT 400 mg/m² on days 1-21. The cycle was repeated every 28 days. The primary end point was Response Evaluation Criteria in Solid Tumors (RECIST) - defined objective response rate. Secondary end points included clinical benefit response (CBR), safety, progression-free survival (PFS), and overall survival (OS). Four single nucleotide polymorphisms in DNA repair genes (RecQ1, RAD54L, XRCC1, ATM) were evaluated whether these influence the clinical outcome. Results: Between December 2006 and February 2008, fifty-one patients were enrolled, with a median age of 58 years. The majority of patients (76%) had intra-hepatic disease. Fourteen patients (27%) had a RECIST investigator-assessed, partial response (PR); disease control rate (PR + stable disease) was 55%. Hematologic toxicity was main grade 3 or 4 treatment-related adverse events. Median PFS was 4.0 months (95% CI, 2.9 to 5.1 months). Median OS was 9 months (95% CI, 5.4 to 12.6 months). XRCC1 R194W had a significant impact on the PFS with log-rank P values of .013. Conclusion: FDR gemcitabine and UFT demonstrated apparent activity in patients with advanced bile duct cancer. Therapy was well tolerated with manageable toxicities. Polymorphic variants of DNA repair genes may affect clinical outcome of patients with advanced bile duct cancer. Keywords: Bile duct cancer, Gemcitabine

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Selection of Patients Who Could Most Benefit from Maintenance Therapy in Non-small Cell Lung Cancer

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Background: Prospective studies have implied that maintenance therapy for non-small cell lung cancer (NSCLC) had its effect by giving active drugs earlier to patients who otherwise die without receiving second-line therapy. The purpose of this study was to select NSCLC patients who could most benefit from maintenance therapy, by evaluating which patients would be less likely to receive second-line therapy. Methods: Clinicopathologic data of advanced NSCLC patients who received four cycles of first-line chemotherapy followed by a certain time of off-therapy and eventual disease progression or death were reviewed retrospectively. Patients were grouped into one with first-line therapy only or the other with further than first-line therapy. Survival and clinical characteristics between two groups were compared. Results: A total of 271 patients were eligible for analysis, and 39 patients (14%) could not receive second-line therapy at any point. Patients with clinical characteristics, such as performance status 2-3 after first-line therapy, large volume of initial target lesions...
Pretreatment FDG-PET Can Predict Survival Rates Following Definitive Radiotherapy in Lymph Node Positive Non-Small Cell Lung Cancer Patients

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Background: For non-small cell lung cancer (NSCLC), [¹⁸F] fluorodeoxyglucose positron emission tomography (FDG-PET) scan has been considered useful in the staging and the radiotherapy (RT) planning. However, the role of FDG-PET for NSCLC has remained controversial as a prognostic predictor. In this study, we investigated whether the maximum standardized uptake value of FDG-PET ratio of lymph node to primary tumor (mSUVR) could be a prognostic factor for lymph node positive NSCLC patients treated with definitive RT. Methods: A total of 68 NSCLC T1-4, N1-3, M0 patients underwent FDG-PET before RT. The radiation field encompassed primary tumor and enlarged or hypermetabolic lymph nodes. Optimal cut-off values of mSUVR were chosen based on distant metastasis-free survival (DMFS) and overall survival (OS). Independent prognosticators were identified by Cox regression analysis. Results: Median follow-up for surviving patients was 18 months (range, 4 to 66 months). With respect to DMFS and OS, the most significant cutoff value for mSUVR was 0.9. The 2-year DMFS was 30% for patients with mSUVR > 0.9 and 50% for those with mSUVR < 0.9 (p=0.04). Two year OS was 23% and 38% respectively (p<0.01). In a multivariate analysis, including age, performance status, stage, use of chemotherapy, and mSUVR, only stage IIB (p=0.05) and mSUVR>0.9 (p=0.01) were significant predictors of OS. The 2-year survival for patients with both stage other than IIB and mSUVR < 0.9 was significantly better than that for patients with either stage IIB or mSUVR>0.9 (DMFS 72% versus 31%, p=0.02; OS 77% versus 15%, p<0.01). Conclusion: Our results suggested that the mSUVR was the strong prognostic factor among the patients with lymph node positive NSCLC following RT. The addition of mSUVR to stage identifies a subgroup of patients at highest risk for death as a result of distant metastasis after RT.

Keywords: Maintenance therapy, Non-small cell lung cancer, Radiotherapy, FDG-PET, Prognosis

Impact of Environmental Tobacco Smoke on the Incidence of Mutations in Epidermal Growth Factor Receptor Gene in Never Smoker Patients with Non-small Cell Lung Cancer

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Background: Active tobacco smoking has been associated with the incidence of EGFR mutations. However, the impact of environmental tobacco smoke (ETS) on EGFR mutations has been unknown. We investigated an association between ETS exposure and EGFR mutations in never smokers with non-small cell lung cancer (NSCLC). Methods: We enrolled 179 consecutive never smokers who were newly diagnosed with NSCLC. The history of ETS exposure was obtained with a standardized questionnaire that included exposure period, place, and duration. The nucleotide sequences of exons 18-21 on EGFR gene were determined using nested PCR amplification. Results: The incidence of EGFR mutations was significantly lower in patients with ETS exposure than in those without (38.5% vs. 61.4%; P=0.008). In a logistic regression model that adjusted for gender and histology, an adjusted odds ratio (AOR) for the risk of EGFR mutations with exposure to ETS was 0.40 (95% confidential interval [CI], 0.20-0.81; P=0.011). In quartile groups based on total smoker-year, the AORs for the lowest- to highest-quartile groups were 0.59 (95% CI, 0.23-1.49), 0.50 (0.17-1.50), 0.48 (0.20-1.18), and 0.22 (0.08-0.62) (P trend=0.028). Among the types of ETS exposure, adulthood ETS and household ETS were significantly associated with the incidence of EGFR mutations. Patients with ETS exposure showed a lower response rate to EGFR tyrosine kinase inhibitors than did patients without ETS exposure (24.6% vs. 44.8%; P=0.053). Conclusion: ETS exposure is negatively associated with EGFR mutations in never smokers with NSCLC.

Keywords: Non-small cell lung cancer, Epidermal growth factor receptor, Environmental tobacco smoke

Distinct Clinico-pathologic Characteristics of Non-small Cell Lung Cancer Patients with ALK Rearrangement: EGFR Mutations and ALK Rearrangement Are Not Mutually Exclusive
Background: The fusion of EML4-ALK gene is created by inv(2)(p21)p23 in lung cancer cells, and this fusion gene accompanies oncogenic potential in mouse model. ALK gene rearrangement is of a great concern because ALK inhibitor has been reported to have considerable efficacy both at preclinical and clinical level. So, we intended to screen clinically operable NSCLC patients for ALK rearrangement using immunohistochemistry (IHC) and ALK break-apart fluorescent in situ hybridization (FISH) to check feasibility of IHC and FISH. We also planned to define the clinico-pathologic characteristics of ALK rearrangement in this population.

Methods: Three hundred and four consecutive patients were included in this study. We used immunohistochemistry to screen ALK protein expression on tissue microarray in duplicate. Then we performed ALK break-apart fluorescent in situ hybridization (FISH) to confirm ALK rearrangement. Clinico-pathologic characteristics including EGFR mutations were evaluated and analyzed according to the ALK rearrangement status. ALK FISH was considered positive when 5% of 200 cells analyzed showed splitting apart of the fluorescent probes flanking the ALK locus. IHC was considered positive if moderate staining was identified in greater than 25% of tumor cells.

Results: This study included 219 males and 85 females with a median age of 62 years. 207 patients had a history of smoking. 131 patients had stage I, 69 patients had stage II, 63 patients had stage IIIa, 36 patients had stage IIIb and 5 patients had stage IV disease. For histology, this study included 136 patients with adenocarcinoma and 126 patients with squamous cell carcinoma. The expression of ALK protein was positive in 9 (3%) of 301 patients. ALK break-apart FISH results were available for 9 ALK IHC positive patients and 22 ALK IHC negative patients. For these 31 patients, ALK FISH showed perfect correlation with ALK IHC. ALK break-apart FISH was positive in 9 ALK IHC positive patients (100%) and negative for 22 ALK IHC negative patients (0%). ALK positive patients had adenocarcinoma histology. None of ALK IHC positive patients had EGFR FISH positivity. Compared to ALK negative patients, ALK positive patients had more frequent adenocarcinoma histology (versus non-adenocarcinoma histology) (p=0.004), were more frequently female (p=0.017) and had high TTF-1 positivity (p=0.001).

Age, smoking status, stage and tumor grade was not different according to ALK IHC status. The EGFR FISH positive rate between ALK IHC positive and negative were not significantly different (p=0.119). For 9 ALK positive patients, 2 had EGFR mutation and 7 were EGFR wild type. Specifically, one patient had nucleotide substitution T2153C of EGFR exon 18 (amino acid Leu718Pro) and the other patient had deletion 2235-2249 of EGFR exon 19.

Conclusion: ALK expression correlated well with ALK rearrangement. Patients with ALK rearrangement had distinct clinic-pathologic characteristics. ALK rearrangement and EGFR mutations were not mutually exclusive.

Keywords: Non-small cell lung cancer, ALK, Rearrangement
to 4 toxicity was neutropenia (34.1% for DC arm; 23.8% for D arm). The result of QoL will be presented. **Conclusion:** Although docetaxel plus carboplatin was well-tolerated and showed modest activity for the patients with old age or poor performance in advanced NSCLC, it failed to show superiority in survival compared with docetaxel.

**Keywords:** NSCLC, Docetaxel, Carboplatin

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**O-18**

The Efficacy of 18FDG-PET Scan One-month after Definitive Radiotherapy in Nasopharyngeal Carcinoma

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**Background:** Positron emission tomography (PET) has been used as an early and accurate tool for response evaluation after definitive radiotherapy (RT) in head and neck cancer. We evaluated the efficacy of the PET with 2-[18F] fluoro-2-deoxy-D-glucose (FDG) one month after definitive RT in patients with nasopharyngeal carcinoma.

**Methods:** Eighty-seven patients who underwent FDG-PET scans before and after radiotherapy for localized nasopharyngeal carcinoma at the Asan Medical Center between August 2001 and December 2006 were retrospectively reviewed. The first FDG-PET scans were performed within 2 weeks before the start day of RT, and second FDG-PET scans were performed 1 month after the completion of RT. FDG-PET images were analyzed by maximal standard uptake value (mSUV). Lesions with 3 or more of mSUV were considered as suspected residual tumors and confirmed by biopsy or were closely observed. All patients were followed for more than 6 months or death. For evaluating the efficacy of the one month FDG-PET scans, the sensitivity, specificity, positive and negative predictive values of the locoregional failure were calculated.

**Results:** The median follow-up time was 39 months (range, 6-87 months). The median mSUV of pre-RT primary site and node were 6.7 and 4.3, respectively (range, 2.0-26.7, basal status-16.0), while median mSUV of post-RT primary site and node were 1.4 and basal status (range, basal status-4.7, basal status-3.7). The overall sensitivity, specificity, positive and negative predictive values of the one month FDG-PET in local failure were 28.6%, 92.5%, 25%, 93.7% and the values for the regional failure were 0.0%, 97.4%, 0.0% and 88.2%, respectively. **Conclusion:** Low maximal standard uptake value (mSUV<3) on the FDG-PET scan one month after definitive RT have a high predictive value of the locoregional disease-free status in nasopharyngeal carcinoma. For patients with clinically equivocal residual lesion but a low mSUV on 1-month post-RT PET scan, close observation can be a safe option without further salvage treatment.

**Keywords:** FDG-PET, Radiotherapy, Nasopharyngeal carcinoma, Standard uptake value

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**O-19**

Tailored-Dose Capecitabine Chemotherapy as Adjuvant Treatment in Elderly Colon Cancer Patients

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**Background:** Elderly patients with curatively resected colon cancer (CC) receive adjuvant chemotherapy less frequently and show poorer compliance than young patients. The dosage of capecitabine in elderly patients is still controversial. Although the capecitabine dosage of 2000 mg/m²/day (days 1-14, every 3 weeks) is commonly used in elderly patients with various solid tumors, fixed-dose reduction in all patients may compromise the effect of adjuvant treatment. Therefore, in this study, we analyzed the feasibility of tailored-dose capecitabine therapy and its effect on treatment compliance and toxicities in elderly CC patients.

**Methods:** Elderly CC patients (>70 years) who had received adjuvant capecitabine monotherapy were consecutively enrolled. Eight cycles of capecitabine was planned. The starting dosage of capecitabine was 2000 mg/m²/day (days 1-14, every 3 weeks). On the second cycle, the dosage was escalated to 2500 mg/m²/day if the patient was tolerable to the first cycle. **Results:** Eighty-six patients were prospectively enrolled and 603 cycles of capecitabine was administered. Median age was 75 years (range: 70-90). Fifty-eight patients (67%) had Eastern Cooperative Oncology Group (ECOG) performance status (PS) grade 0/1 and 28 patients (33%) had ECOG PS grade 2, respectively. Sixty-eight patients (79%) completed 8 cycles of chemotherapy. Fifty-nine patients (69%) could complete the escalated dose of capecitabine at the second cycle and 24 patients (28%) could complete the 8 cycles of escalated dose. Severe hematologic toxicities (per cycle) included grade 3/4 neutropenia (0.8%) and thrombocytopenia (0.2%). Severe non-hematologic toxicities (per patient) included grade 3/4 hand-foot syndrome (24%), anorexia (6%) and diarrhea (6%). **Conclusion:** The tailored-dose approach is feasible and may be more appropriate for elderly CC patients than indiscriminate fixed-dose approach to avoid unnecessary dose reduction and increased toxicities.

**Keywords:** Elderly, Colorectal cancer, Adjuvant chemotherapy, Capecitabine

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**O-20**

Clinical Impact of Microsatellite Instability in Colon Cancer following Adjuvant FOLFOX Therapy
Significance of Cyclooxygenase-2 in Predicting Clinical Outcome of Locally Advanced Rectal Cancer Patients Treated with Postoperative Adjuvant Chemoradiation

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Background: To determine whether overexpression of cyclooxygenase-2 (COX-2) is an indicator of prognosis in patients with locally advanced rectal cancer undergoing surgical resection and postoperative adjuvant chemoradiation. Methods: Seventy two patients with locally advanced rectal cancer who were treated with surgical resection and postoperative adjuvant chemoradiation between 2000 and 2001 were divided into two groups according to their COX-2 levels in an immunohistochemical study: the COX-2 (+) group (n=27) and the COX-2 (-) group (n=45). The specimens were graded based on the intensity and extent of staining. The correlations between COX-2 overexpression and clinicopathologic parameters, patterns of failure and survival were analyzed. Results: Median follow up period was 65 months. COX-2 overexpression was observed in 37.5% of patients. The COX-2 (+) group showed significantly higher treatment failure rates compared with the COX-2 (-) group. Pelvic failure rates were 25.9% for the COX-2 (+) group and 6.7% for the COX-2 (-) group (p=0.02). Distant metastases were observed in 48.1% of the COX-2 (+) group and 17.8% of the COX-2 (-) group (p=0.006). Five-year actuarial overall survival rates were 54.1% for the COX-2 (+) group and 85.6% for the COX-2 (-) group (p=0.03). Five-year disease free survival rates were 46.8% for the COX-2 (+) group and 76.0% for the COX-2 (-) group (p=0.02). Univariate and multivariate analyses showed that COX-2 overexpression was an independent prognostic factor that surpassed other well-known clinicopathologic parameters. Conclusion: COX-2 overexpression can be used as a potent molecular risk factor in patients with locally advanced rectal cancer treated with surgical resection and postoperative adjuvant chemoradiation.

Keywords: Cyclooxygenase-2, Rectal cancer, Prognostic factor, Adjuvant pelvic chemoradiation

High Number of Tumor-infiltrating FOXP3-Positive Regulatory T-cells Are Associated with Im-
Background: This study evaluated the association of tumor-infiltrating T-cell subsets with clinical outcomes after chemotherapy in patients with ocular adnexal lymphoma of mucosa-associated lymphoid tissue type (OAML). Methods: Pre-treatment formalin-fixed paraffin-embedded tissues from 25 patients with OAML, who had received first-line combination chemotherapy between 1989 and 2006, were stained with CD3, CD4, CD8, and FOXP3 monoclonal antibodies. The amount of tumor-infiltrating T-cell subsets were numerically quantified by image analysis program.

Results: The median age was 53 years (range, 18-78 years) with a male:female ratio of 4:1. Patients received combination chemotherapy including cyclophosphamide, vincristine, and prednisolone (CVP, n=16), doxorubicin, vincristine, and prednisolone (DVP, n=8), or cyclophosphamide, doxorubicin, vincristine, and prednisolone (DOVP, n=1). After a median follow-up of 44 months, median progression-free survival (PFS) was 67 months and overall response rate was 88% (complete remission [CR], 52%). High number of tumor-infiltrating FOXP3-positive regulatory T-cells (Tregs) was significantly associated with higher CR rate (75% vs 31%, P=0.027), and longer PFS (79 vs 34 months, P=0.010). When the analysis was limited to the patients who had received CVP regimen (n=16), high number of Tregs also significantly related to longer PFS (79 vs 17 months, P=0.034). Conclusion: High number of tumor-infiltrating Tregs predicts improved clinical outcomes in OAML patients treated with chemotherapy.

Keywords: Marginal zone B-cell lymphoma, FOXP3, Regulatory T-lymphocytes, Prognosis

Cancer Pain Management with Hydromorphone OROS in Korean Cancer Patient: Evaluation of Its Clinical Usefulness in Reduction of Breakthrough Pain Medication Frequency: Multicenter, Prospective, Open-label Study

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Background: A majority of patients with cancer experience cancer pain of higher than moderate severity during the progression of cancer. Of these, 2/3 of patients with cancer have been reported to be inflicted with breakthrough pain. Methods: The primary objective is to evaluate the clinical usefulness of hydromorphone OROS tablet in reduction of breakthrough pain medication frequency in Korean patients. This study enrolled only patients who took immediate-release analogics more than twice a day on average for the treatment of breakthrough pain during a 3-day period prior to Visit 2. For seven days (±1) since Visit 2, based on the dose at which analogics were administered, hydromorphone OROS tablet (test drug) with an equivalent profile of the analgesic effectiveness was administered after the dose was determined. For an initial dose of the test drug, the dose of previous analogics was converted to a daily dose of oral morphine. Thus, the dose of test drug with an equivalent profile of the analgesic effect was determined. Results: The frequency of the use of immediate-release analogics for the management of breakthrough pain was decreased from 3.05 times to 1.99 times (p<0.001). The incidence of breakthrough pain was also decreased from 4.2 times to 2.6 times (p<0.001). K-BPI score was also decreased from 3.6 to 3.2 with 11.1% reduction. In 63% of patients and 62% of physicians, there was a satisfaction with the pain treatment. In regard to the preference to test drug in 90.3% of patients who completed the treatment, 81% of patients preferred test drug because ‘the cancer pain could be controlled with a one-time treatment’ and 35% of patients preferred the test drug because’ the use of immediate-release analogics could be diminished for the management of breakthrough pain’. In 87.2% of patients who used analogics, the side effects occurred in such an order as constipation, drowsiness and dizziness. But there were no cases of uncontrolled specific side effects. Conclusion: A 24-hr sustained-release type of hydromorphone OROS tablet significantly diminished the use of immediate-release analogics and the incidence of breakthrough pain.

Keywords: Cancer pain, Breakthrough pain, Hydromorphone

A Cross-Sectional Study of Imatinib Plasma Trough Levels in Patients with Advanced Gastrointestinal Stromal Tumors: Impact of Gastrointestinal Resection on Exposure to Imatinib

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**Background:** Imatinib (IM) trough plasma levels (Cmin) have been reported to correlate with treatment outcomes in patients with gastrointestinal stromal tumors (GISTs). We have therefore evaluated the correlation between IM Cmin and the clinical characteristics of patients with GISTs.

**Methods:** IM Cmin at steady state was measured in 107 GIST patients on IM. Blood samples were collected prior to the morning dose (mostly 22-26 hours after previous dose). Two measurements were obtained at two different times. The plasma IM level was measured by liquid chromatography-tandem mass spectrometry. In 92 patients treated with 400mg/day, IM Cmin was correlated with age, body weight, body surface area (BSA), duration of imatinib use, previous surgical type, hemoglobin, white blood cell counts (WBC), platelet, and serum albumin at the time of blood sample by using linear regression and Mann-Whitney test. **Results:** In patients treated with 400 (n=92), 300 (n=7), 600 (n=2), or 800 (n=11) mg/day IM, the IM Cmin was 1305±633 ng/mL, 1452±830 ng/mL, 1698±725 ng/mL, and 3330±1592 ng/mL, respectively. Of the 92 patients treated with 400 mg/day IM, 25 (27%) received IM as adjuvant therapy after curative resection and 67 (73%) as primary therapy for advanced disease. Of these 92 patients, 59 (63%) were men; median age was 55 years (range, 28-76 years) and median duration of IM use before sampling was 8.8 months (range, 0.5-67.6 months). The mean inter- and intra-subject variability was 44.7% and 26.5%, respectively. In univariate analyses, high Cmin was correlated with advanced age (p=0.02), low creatinine clearance (p=0.001), low hemoglobin (p=0.01), and albumin (p<0.001) concentrations. IM Cmin was also significantly lower in patients with (n=17, 937±339 ng/mL) than without (n=75, 1388±656 ng/mL) major (total or subtotal) gastrectomy (p=0.002). Body weight, body surface area, WBC, other types of surgery (minor gastrectomy, small bowel resection, or hepatic resection) and duration of IM use were not associated with IM Cmin. **Conclusion:** In patients with GISTs, IM Cmin at steady state was significantly associated with albumin concentration, creatinine clearance and previous major gastrectomy. Although its clinical impact is unclear at present time, monitoring of imatinib Cmin might be particularly important for optimal treatment with imatinib in patients who have undergone major gastrectomy.
Poster Presentation
MDR1/ABCB1 Single Nucleotide Polymorphism (SNP) in Stage II/III Breast Cancer Patients Who Received Docetaxel and Doxorubicin Neoadjuvant Chemotherapy

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Background: Expression of the adenosine triphosphate-binding cassette B1 (ABCB1) transporter, which is also called P-glycoprotein, is known to be associated with resistance to anticancer drugs. The aim of this study was to investigate clinical impact of genetic polymorphisms of MDR1/ABCB1 gene in patients with breast cancer who were treated with neoadjuvant chemotherapy.

Methods: Stage II or III breast cancer patients who referred for neoadjuvant chemotherapy were enrolled between September 2003 and August 2008. Patients were treated with 3 cycles of docetaxel and doxorubicin neoadjuvant chemotherapy. The clinical response was determined by RECIST criteria after 3 cycles of neoadjuvant chemotherapy, after which the patients received curative surgery. Patients who did not experience progression during the neoadjuvant chemotherapy, underwent additional 3 cycles of adjuvant chemotherapy with the same regimen. Adjuvant hormonal therapy and radiation therapy were given when indicated. Single nucleotide polymorphisms of MDR1/ABCB1 (C3435T, G2677T/A, and C1236T) gene were genotyped using baseline peripheral blood mononuclear cells. The correlation of genetic polymorphisms of MDR1/ABCB1 and clinical outcome was analyzed.

Results: A total of 216 patients were enrolled. The median age was 44 years (range 25-69 years), the median primary tumor size was 5.7 cm (range 2.0 to >12.0 cm) with 82.0% ≤stage IIIA, 50.0% of T3/T4, and 56.5% of N2 or 3 stage. With regard to hormonal status, 45.8% was ER+, 33.8% PR+, 31.0% HER2+, and 31.5% triple negative. The overall radiologic response rate (RR) was 76.9%, while 83.8% of patients achieved a pathologically complete response. After a follow-up duration of 37.3 months, median relapse free survival (RFS) and overall survival (OS) were not reached. There was a trend toward longer overall survival (p=0.075) and lower relapse rate (p=0.188) in patients with TT genotype than in those with CC/CT genotype, although which did not reach statistical significance. Polymorphisms of G2677T/A or C1236T were not associated with clinical outcomes in terms of response rate and survival.

Conclusion: Our study suggested that genetic polymorphism of MDR1/ABCB1 C3435T might be associated with clinical outcomes in patients treated with neoadjuvant docetaxel/doxorubicin for stage II and III breast cancer. Further research including functional analysis and longer follow-up duration is warranted to clarify the clinical impact of MDR1 gene polymorphisms.

Keywords: Breast cancer, Neoadjuvant chemotherapy

Predictive Factors for Pathological Complete Response (pCR) after Preoperative Chemotherapy in 338 Patients with Stage II, III Breast Cancer

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Background: We evaluated clinicopathological features to define predictive factors for pCR, a surrogate marker for clinical outcomes, in the stage II, III breast cancer patients (pts).

Methods: Between 2001 and 2008 at the National Cancer Center Hospital, 338 pts underwent preoperative chemotherapy as follows: AC (doxorubicin/cyclophosphamide), 101 pts; TX (docetaxel/capecitabine), 103 pts; PG (paclitaxel/gemcitabine), 43 pts and AT (doxorubicin/docetaxel), 91 pts. pCR is defined as no residual invasive carcinoma in the breast.

Results: Median age was 44 (range, 21-76) years with 75% premenopausal, 58% ER+, 50% PR+ and 33% HER2+. There were 43% ER or PR+/HER2- tumors, 18% ER or PR+/HER2+ tumors, 15% ER-/PR-/HER2+ tumors, and 23% ER-/PR-/HER2- tumors among 336 tumors known for all three receptor (ER, PR, HER2) status. Overall 16% of all patients achieved pCR: 10% of pts with ER or PR+/HER2-, 13% with ER or PR+/HER2+, 33% with ER-/PR-/HER2+, and 19% with triple negative tumors (p=0.001). In univariate analysis, higher histologic grade (p=0.008), ER negativity (p=0.000), PR positivity (p=0.003), Hormone receptor negativity (p=0.001), HER2 positivity (p=0.028), and breast cancer subtype (p=0.001), clinical complete response (p=0.014) were significant variables. In multivariate analysis, age <50 years (p=0.009), higher histologic grade (p=0.040), negative hormone receptor status (p=0.024), HER-2 positivity (p=0.007) and breast cancer subtype (p=0.019) remained as significant variables.

Conclusion: Patients with ER-/PR-/HER2+ tumors achieved significantly higher pCR rate as compared with other subtypes (p=0.001). Younger age and higher histologic grade, negative hormone receptor, HER-2 positivity, breast cancer subtype were significant predictive factors for high pCR rate in this study. Partly supported by NCC Grant No 0610240.

Keywords: Breast cancer, Predictive factor, Neoadjuvant chemotherapy
An Observational Study of Docetaxel-Based Adjuvant Chemotherapy in Breast Cancer Patients at High Risk of Recurrence in Asia-Pacific

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Background: This observational study (registry) aims to assess patient profile and pattern of care in operable breast cancer (BC) patients at high risk of recurrence treated with docetaxel-based adjuvant chemotherapy in Asia-Pacific countries.

Methods: Newly diagnosed female BC patients aged >18 years were enrolled from December 2006. Post-enrollment assessments included: demographics, medical history, BC stage and biologic characteristics, curative surgery and chemotherapy plan, and adverse events (AEs). No experimental intervention was imposed, treatment was determined by the treating physician. Data presented reflect the second interim analysis at 3 years. Further follow-up will be at 5 years postenrollment.

Results: 1,537 patients were enrolled in 10 countries: Taiwan (n=432); Korea (n=417); China (n=327); Hong Kong (n=147); Vietnam (n=69); Philippines/Singapore (n=64); Pakistan (n=39); Bangladesh/India (n=42). Mean age was 47.7 years (range: 23-83); 52.4% (n=804) were premenopausal, and 38.8% (n=595) postmenopausal. Most patients (97.4%, n=1495) had high or intermediate risk of recurrence. 59.3% (n=910) were ER positive; 43.1% (n=662) were HER2 positive. Total mastectomy was the most common surgical intervention (72.6%, n=1116) and sequential docetaxel therapy was the most frequently administered adjuvant chemotherapy (56.5%, n=860), followed by combination therapy (38.2%, n=581) and other regimens (13.5%, n=68). 8.0% of patients received concomitant granulocyte-colony stimulating factor (mean 3.6 cycles).

Conclusion: Interim findings of this observational study suggest that sequential docetaxel-based adjuvant chemotherapy is a core component of care for Asia-Pacific BC patients at high risk of recurrence.

Keywords: Observational study, Docetaxel, Adjuvant

Global Breast Cancer Trends and Challenges: A South Korean Perspective

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Background: To determine greatest perceived challenges, trends and needs among breast cancer medical, policy and advocacy thought leaders across the world, to identify the opportunities to advance the breast cancer control within and across diverse international countries, and to compare these to perceived challenges and needs among South Korea thought leaders.

Methods: 225 thought leaders associated with breast cancer in 30 countries including Asia, Latin America, and the Middle East participated in a comprehensive survey using horizon scanning methodology. Key informant interviews included medical oncologists, surgeons, other breast cancer specialists, advocate leaders and cancer policy makers. 20 thought leaders participated from South Korea (18 medical thought leaders, 1 public policy, 1 advocacy leader).

Results: Across all 30 countries, 47% of respondents identified a major challenge to be the ability to provide personalized therapy. 46% identified the need for increased numbers of trained oncology nurses in breast cancer patient care and education. 45% cited the relatively higher observed proportion of younger women in non-Caucasian populations presenting with more aggressive breast tumors. In comparison, thought leaders in Korea, identified the two most important challenges and needs being trained oncology nurses (40%) and keeping up to date with information (30%). Secondarily, they noted an increasing number of young women diagnosed with highly aggressive tumors.

Conclusion: In South Korea, further basic, clinical and epidemiological research as well as significant increases in the number of oncology nurses should be a priority, and finally, public education and other advocacy efforts are needed.

Keywords: Breast cancer, Trends, Challenges
Skin and Soft Tissue Infiltration Patterns of Breast Cancer according to Subtypes at the Time of Skin Metastases

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Background: Breast cancer is heterogeneous disease with variable morphologic features and biomarkers. It often manifested itself with skin changes at the time of diagnosis or metastasis with- or without soft tissue infiltration. Therefore, we are to evaluate whether skin changes and soft tissue infiltration patterns would be reflect their subtypes according to hormonal receptor (HR) and HER2 status at the time of skin metastases.

Methods: We included the patients who had been performed skin biopsy including immunohistochemical staining for estrogen receptor (ER), progesterone receptor (PR), and HER2 from 1998 to 2008 at Samsung Medical Center. We retrospectively reviewed the patients’ medical records with radiologic image studies (chest CT or breast MRI).

Results: The median age of all 130 patients was 48 (25-79) years old. The numbers of each subtype were as follows: HR+, 55 (42.3%); HER2, 43 (33.1%); TNBC, 32 (24.6%). There was no difference of the patients’ characteristics in terms of age, stage at the initial diagnosis, surgery type, radiation treatment, and metastatic organs among three groups. The presence of ulceration in skin (57% vs 25% vs 19%, p=0.024) and mass formation (62% vs 37% vs 34%, p=0.013) were more frequently observed in HR+ group than the other groups. On the contrary, erythematous patch (19% vs 54% vs 75%, p=0.002) and skin thickening (2% vs 16% vs 13%, p=0.021) were more common in HER2 and TNBC groups than HR+ group. Diffuse infiltration pattern at the imaging study with CT or MRI was also much more common in HER2 and TN group (2% vs 12% vs 19%, p 0.016). The median survival from skin metastases to death was 44 (0-92) months.

Conclusion: The patterns of skin involvement including surrounding soft tissue infiltration may reflect breast cancer subtypes according to HR and HER2 status. Further evaluation whether the difference of the patterns can predict clinical outcomes for the treatments should be warranted.

Keywords: Skin metastasis, HER2, HR

Heterogeneity of Triple Negative Breast Cancer (TNBC): TNBC Might be Divided into Two or More Subgroups by Clinicopathologic Findings

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Background: Breast cancer comprises a heterogeneous group of diseases that vary in morphology, biology, behavior and response to therapy. Triple-negative breast cancer (TNBC) is a subtype of tumors (estrogen (ER), progesterone (PgR), and human epidermal growth factor receptor-2 (HER2) receptor negative) with aggressive clinical behavior which currently lacks effective targeted therapies. TNBC exhibits a distinct pattern of recurrence which is characterized by rapidly rising rate in the first 2 years following diagnosis, a peak at 2-3 years followed by a decline in recurrence risk over the next 5 years. However, some of the TNBC patients show indolent clinical behavior associated with good clinical outcome. This reinforces the notion that TNBC is a heterogeneous group comprising subtypes with different features and clinical outcome. The aim of this study is to classify TNBC into two subgroups at least, each of which has different clinical course and long-term outcome.

Methods: We retrospectively analyzed the clinicopathologic characteristics and outcomes of patients with recurring or metastatic TNBC who received palliative treatment from 1999 to 2007 at Samsung Medical Center.

Results: One hundred and seventy-three patients with recurrent and/or metastatic TNBC, who were available clinical data, were recognized. Of 173 patients, the number of relapsed patients after curative surgery was 154, and remaining were initially metastatic patients. The median recurrence-free survival (RFS) of 154 patients was 23.6 months (95% CI, 20.4-26.8) and the median overall survival from metastasis of all 173 patients was 21.2 months (95% CI, 16.4-26.0). We divided the patients into two groups according to RFS of 36 months. TNM staging did not show any relationship with RFS (median RFS 24, 27, and 21 months for each stage, p=0.135). The TNBC patients who had RFS of 36 months or greater showed better disease control rate (DCR), progression-free survival (PFS) to 1st line palliative chemotherapy and overall survival (OS) than those with RFS of less than 3 years (DCR 55% vs 77%, p=0.022; median PFS 3.6 vs 7.7 months, p=0.0001; median OS 17.4 vs 42.0 months, p=0.0003). The incidence of brain metastases at the time of first metastasis was much more common in patients with shorter RFS than in those with longer RFS (16% vs 3%, p=0.047). Cox-regression multivariate analysis for OS revealed presence of brain metastasis, presence of hepatic metastasis, and RFS of less than 3 years were identified as independent risk factors (HR 2.01, p=0.007 for brain metastasis; HR 1.99, p=0.007 for hepatic metastasis; HR 2.45, p=0.001 for RFS of 3
Trastuzumab Mediated Cardiac Dysfunction Outside Clinical Trials: A Single Center Experience in Asia

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Background: Trastuzumab is an effective drug for the treatment of HER2 positive breast cancer (BC); however, cardiac dysfunction (CDx) has been reported as a major adverse event. The purpose of our study was to investigate the trastuzumab mediated CDx in a practice setting and the treatment outcome at a single Asian center.

Methods: We retrospectively analyzed 129 HER2- overexpressing BC patients (pts) who were treated with a trastuzumab containing regimen between January 2005 and December 2007 at Seoul National University Hospital. We investigated the incidence of CDx and the degree of reversibility using echocardiography (EchoCG) and attempted to identify the risk factors to predict CDx.

Results: In 129 consecutive pts (median age 47; range 25-79), median left ventricular ejection fraction (LVEF) was 59% (range 45-70) measured by EchoCG. Ninety (69%) were palliatively treated and 98 (76%) had previously received anthracycline-based chemotherapy. Median duration of follow-up was 21 months. LVEF decreased more than 10% points in 10 out of 129 (7%). According to the National Cancer Institute Common Terminology Criteria for Adverse Events: left ventricular systolic dysfunction, grade (G) 2 and G 3/4 CDx developed in 4 (3%) and 8 (6%) pts, respectively. Seven (18%) pts experienced symptomatic heart failure (HF). Five pts including 3 with symptomatic HF discontinued trastuzumab, and 3 resumed trastuzumab after median 144 days (95% confidence interval; 127-162) of discontinuation. Median LVEF was 54% (range 45-63) at baseline in pts with symptomatic HF and decreased to 49% (range 33-50) after median 175 days (range 65-415) of trastuzumab treatment. HF treatment was initiated in 9 pts including 6 with symptomatic HF. Four pts received angiotensin converting enzyme inhibitors (ACEI), 3 angiotensin receptor blockers (ARB) and 2 ACEI or ARB with diuretics. The incidence of symptomatic HF was associated with lower baseline LVEF (≤55%, p=0.014). Though higher anthracycline cumulative dose (≥200 mg/m2) was noted with higher occurrence of symptomatic HF, it was not statistically significant. In the pts with symptomatic HF, LVEF was restored to 53% (range 42-59) which was similar to baseline at median 168 days (range 56-406) after the diagnosis of CDx.

Conclusion: The majority of pts with trastuzumab-associated CDx were asymptomatic and CDx was reversible.

Keywords: Breast cancer, Trastuzumab, Cardiac toxicity

Phase II Study of Irinotecan Plus Capecitabine in Patients with Anthracycline and Taxane Pretreated Metastatic Breast Cancer

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Background: To assess the objective response rate (RR) of irinotecan(I) and capecitabine (X) combination in metastatic breast cancer (MBC) patients (pts) was the primary end point.

Methods: Anthracycline- and taxane-pretreated pts with measurable disease, age ≥18 years, adequate organ functions, and ECOG performance score (PS) 0-2 were eligible. Pts received I 80 mg/m2 intravenously on days 1 and 8 and X 1,000 mg/m2 orally twice daily on days 1-14 of every 21-day cycle.

Results: Between Sept 2006 and Apr 2008, 36 pts with median age of 50 years (range, 28-71) were enrolled. Median follow-up was 17 months (range, 8.3-18.7). Among 35 evaluable pts excluding 1-consent withdrawal, 86% received at least one prior chemotherapy for MBC; 20% had stage IV disease with 66% lung/ 37% liver metastases; 80% had PS 0-1; 74% had hormone receptor (HR) positive tumors, 20% triple negative disease and 3% HER2 positive tumors. Overall RR was 60% (95% CI, 43.5-74.5) with median response duration of 6.3 months (range, 1.0-21.1+); 2 CR (6%), 19 PR (54%), 8 SD (23%) and 6 PD (17%) with similar RR between HR+ (63%) vs triple negative disease (57%). Median survival was not reached with 76% estimated survival at 1-year, and median progression free survival (PFS) was 7.3 months (range, 0.7-21.1+). Pts received a median of 8 cycles of treatment (range, 1-26+). G1, G2 and G3 hand-foot syndrome were observed in 34%, 17% and 0%, respectively. NCI Grade ≥3 adverse events were: neutropenia (60%); asthenia, diarrhea, and vomiting (9%, each); transaminase elevation and febrile neutropenia (6%, each); abdominal pain, anorexia, fatigue, myalgia, and nausea (3%, each).

Conclusion: I and X combination by this schedule and doses is highly efficacious in anthracyline- and taxane-pretreated MBC pts with manageable toxicities. Further investigation of this combination in phase III trials is warranted.

Supported
Predictors of 4 or More Positive Axillary Nodes in Patients with Node-positive T1-2 Breast Carcinoma: The Indications for Adjuvant Irradiation of the Level III Axilla and Supraclavicular Fossa

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Background: We evaluate the predictors of 4 or more involved axillary nodes in 286 patients with node-positive T1-2 breast carcinomas to select a group of patients who are indicated for adjuvant irradiation of the level III axilla and supraclavicular fossa (SCF).

Methods: We have reviewed the database of all the patients who were diagnosed with node-positive T1-2 breast carcinomas and who underwent surgery at St. Vincent’s hospital, The Catholic University of Korea College of Medicine between January 2000 and June 2009.

Results: On the multivariate logistic-regression analysis, an increasing tumor size (p=0.001), the presence of LVSI (p<0.001), and a palpable mass (p<0.001) were positively associated with involvement of 4 or more axillary lymph nodes. Our data suggest that for patients with node-positive T1-2 breast cancer, the presence of 4 or more involved nodes is frequent for the patients with an increasing tumor size, the presence of LVSI and a palpable mass at the time of diagnosis.

Conclusion: According to our study, 86.1% of the patients with all the unfavorable factors have involvement of 4 or more nodal metastases, and we recommend them irradiation of the high axilla and SCF for adjuvant care, if they do not undergo complete axillary dissection.

Keywords: Axillary lymph node, Breast cancer, Predictor

Predictive Value of Orotate Phosphoribosyltransferase Expression for Treatment Outcomes in Patients with Advanced Gastric Cancer Treated with 3-weekly S-1 Plus Cisplatin Chemotherapy

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Poster Presentation

P-09

Single Nucleotide Polymorphisms of CYP19A1, rs10459592 and rs4775936 Predict Clinical Benefit of Letrozole in Patients with Metastatic Breast Cancer

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Background: We evaluated the efficacy of an aromatase inhibitor, letrozole in metastatic breast cancer patients according to DNA polymorphisms of the aromatase gene CYP19A1.

Methods: Patients (n=113) with HR+ MBC were treated with letrozole. Monthly GnRH agonist was added in premenopausal patients. DNA was isolated from peripheral blood samples and was genotyped for 50 polymorphisms of CYP19A1 by iPLEX Gold assay based on MALDI-TOF.

Results: Among 50 examined single nucleotide polymorphisms (SNP), 10 SNPs were revealed as monomorphic for Korean population. After trimming of the data using HWE test, rs10459592 (T/G) and rs4775936 (C/T), which were located in exon I.6 of CYP19A, were significantly associated in an over-dominant model with higher disease control rate (CRb) (HR=2.82 [95% CI 1.21-6.10], p=0.0149; HR=2.62 [95% CI 1.12-6.10], p=0.0149; HR=2.61 [95% CI 1.12-6.59], p=0.0149; HR=2.62 [95% CI 1.12-6.10], p=0.0149; HR=2.82 [95% CI 1.12-6.10], p=0.0149; HR=2.82 [95% CI 1.12-6.10], p=0.0149; HR=2.82 [95% CI 1.12-6.10], p=0.0149; HR=2.82 [95% CI 1.12-6.10], p=0.0149; and HR=2.62 [95% CI 1.12-6.10], p=0.0149; respectively). In linkage disequilibrium analysis, these were strongly linked (D'=1.0, r2=0.936), and subsequent haplotype analysis showed a statistical significance with regard to higher disease control rate (HR=2.61 [95% CI 1.12-6.1], p=0.0238). Median time to progression (TTP) with a median follow-up of 85.7 months (range 9.7-107.4 months) was improved in patients having over-dominant form of rs10459592 without statistical significance (median 7.74 months [95% CI 6.48-9.00] vs. median 12.07 months [95% CI 11.19-12.95], p=0.147). In multivariate analysis, patients with HR+ MBC treated with an aromatase inhibitor, letrozole, the presence of SNPs in the exon I.6 of CYP19A1, rs10459592 and rs4775936 were significantly associated with improved treatment efficacy. Although further study is needed, our data present possible candidate markers for the letrozole treatment in metastatic breast cancer.

Keywords: CYP19A1, Single nucleotide polymorphism, Letrozole, Breast cancer

P-10

Predictive Value of Orotate Phosphoribosyltransferase Expression for Treatment Outcomes in Patients with Advanced Gastric Cancer Treated with 3-weekly S-1 Plus Cisplatin Chemotherapy

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by NCC Grant No 0610240-3. Irinotecan was supplied by SHIN POONG PHARM. CO.,LTD.

Keywords: Breast cancer, Irinotecan, Capecitabine
Background: S-1 has recently been shown to improve clinical outcomes of patients with metastatic or relapsed gastric cancer (MRGC), especially when combined with cisplatin. In Japanese patients, 5-weekly regimen [S-1 80 mg/m^2/day (days 1–21) plus cisplatin 60 mg/m^2/day (day 8)] has been commonly used. However, it is still controversial which combination schedule of S-1 and cisplatin is the most appropriate for the improvement of anti-tumor activity and patients’ compliance. Thus, this study was performed to evaluate the efficacy and toxicity of a 3-weekly S-1 plus cisplatin regimen. Predictive value of protein expressions, which are associated with fluoropyrimidine and cisplatin metabolism, was also evaluated.

Methods: Forty-six chemotherapy-naive MRGC patients were consecutively enrolled. S-1 (80 mg/m^2/day) was given orally on days 1–14 and cisplatin (60 mg/m^2) was administered i.v. on day 1. All patients had Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0–2 and had at least one measurable lesion. Expression levels of thymidylate synthase (TS), dihydropyrimidine dehydrogenase (DPD), thymidine phosphorylase (TP), orotate phosphoribosyltransferase (OPRT), excision repair cross-complementation 1 (ERCC1), Fanconi anemia complementation group D2 (FANCD2), glutathione S-transferase-P (GSTP), and X-ray repair cross-complementing group 1 (XRCC1) were determined by immunohistochemical staining.

Results: The median age of enrolled patients was 61 years. Overall response rate was 48%; one patient (2%) showed complete response and 21 patients (46%) had partial responses. The median progression free survival (PFS) and overall survival (OS) were 21.1 and 68.3 weeks, respectively. Common hematologic toxicities were anemia (93%) and neutropenia (61%). However, grade 3/4 anemia and neutropenia developed only in 11% and 24%, respectively. Common non-hematologic toxicities were anorexia (70%), nausea (63%), asthenia (57%), vomiting (39%), stomatitis (41%) and diarrhea (35%). Grade 3/4 non-hematologic toxicities included anorexia (22%), asthenia (13%), nausea (7%), and diarrhea (7%). The expression level of OPRT was classified into 2 groups based on intensity and percentage of stained cancer cells. Patients with higher OPRT levels in tumor tissue had superior PFS [23.3 vs. 14.1 weeks (median)] and OS [72.4 vs. 55.4 weeks] to those with lower OPRT levels. Expression levels of other proteins were not predictive of treatment outcomes. In multivariate analysis, both ECOG PS ≤1 (vs. 2) and higher OPRT levels (vs. lower levels) were independently associated with prolonged PFS and OS (p < 0.05).

Conclusion: This 3-weekly combination of S-1 and cisplatin is active and well-tolerated in MRGC patients. OPRT levels in tumor tissues may be predictive of treatment outcomes.

Keywords: S-1, Cisplatin, Gastic cancer, Orotate phosphoribosyltransferase

Expression of Bax Predicts Outcome in Advanced Gastric Cancer Patients Treated with 5-Fluourouracil, Leucovorin and Oxaliplatin Palliative Chemotherapy

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Background: The enhancer of zeste homolog 2 (EZH2), a member of the polycomb group of proteins, plays an important role in cell proliferation and cell cycle regulation. EZH2 is overexpressed in aggressive forms of prostate, breast, bladder, and endometrial cancers. However, the role of EZH2 expression in gastric cancer has not been fully determined. This study was conducted to investigate the mechanisms of carcinogenesis and the clinical value of EZH2 expression in gastric cancer.

Methods: We analyzed EZH2 expression by Western blotting in AGS, MKN-28, SNU-16, SNU-484, SNU-601, and SNU-638 gastric cancer cell lines. After transfection of EZH2 siRNA into MKN-28 cells, the change in cell cycle-related molecules was assessed by Western blot. Expression of EZH2, Ki-67, and p53 was determined by immunohistochemical staining of tissue microarrays from specimens of 137 cases of resected gastric cancer.

Results: We found high expressions of EZH2 in all of the tested gastric cancer cell lines. RNA interference of EZH2 induced upregulation of p53 and HDAC1 and down-regulation of cyclin D1 and cyclin E. High EZH2 expression was observed in 60.6% of gastric cancers and in 6.7% of non-neoplastic gastric tissues (p < 0.01); 40.1% were positive for p53 in gastric cancers. High EZH2 expression was correlated with Ki-67 and p53 expressions and was significantly associated with distant metastases and non-signet ring cells.

Conclusion: Our results suggest that high EZH2 expression is associated with tumor cell proliferation and metastasis in gastric cancers.

Keywords: EZH2, Gastric cancer, Ki-67, p53
Background: The present study evaluated the prognostic significance of Bax, excision repair cross-complementation group 1 (ERCC1), and thymidylate synthase (TS) in advanced gastric cancer patients treated with 5-FU, leucovorin, and oxaliplatin (FOLFOX) palliative chemotherapy.

Methods: Seventy-two patients with metastatic or recurrent gastric cancer were treated with FOLFOX regimen. Pre-treatment tumor biopsy specimens were analyzed for Bax, ERCC1, and TS expression by immunohistochemistry.

Results: High expression of Bax, ERCC1 and TS was observed in 31 (43%), 33 (46%), and 35 (49%) patients, respectively. The median overall survival (OS) of patients was 12 months. Low expression of Bax was associated with poor OS (median, 9 months vs. 18 months; 2-year, 10% vs. 48%; p=0.0005) in univariate analysis, while expression of ERCC1 and TS was not correlated with patient outcome. In multivariate analysis, low expression of Bax was a significant independent predictor of poor OS (p=0.029).

Conclusion: Low expression of Bax was significantly associated with the poor survival of patients with metastatic or recurrent gastric cancer treated with FOLFOX chemotherapy. Immunohistochemical staining for Bax with pretreatment biopsy specimen may be a useful in selecting FOLFOX regimen as a treatment option for advanced gastric cancer patients.

High SUV in FDG PET/CT Predicts Worse Prognosis in Metastatic Gastric Cancer Patients Receiving Palliative Chemotherapy

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Background: We evaluated the role of FDG PET/CT in metastatic gastric cancer patients in terms of chemoresponsiveness and survival.

Methods: From April 2006 to December 2008, newly diagnosed metastatic gastric cancer patients in Konkuk University Hospital, histologically diagnosed as non-signet ring cell adenocarcinoma were enrolled in this study. FDG PET/CT was checked before 1st line palliative chemotherapy.

Results: A total of 35 patients (11 females, 24 males; age 57±13 yr) were enrolled in the study. FDG-PET/CT visualized all the primary tumors (mean SUVprimary=8.1±4.5, range: 2.5-22.1). SUVprimary were 9.1±5.4 in PR group, 6.5±0.9 in SD group, and 8.7±2.1 in PD group (no difference). Median overall survival was 9.7 mo (range: 1.6-22.2 mo). Log rank test showed that ECOG performance status (PS) ≥2, presence of solid organ metastasis, number of metastatic sites ≥2, and SUVprimary ≥8.0 were poor prognostic factors. By multivariate analysis, SUVprimary ≥8.0 (OR 2.56, p=0.035) was an independent poor prognostic predictor together with ECOG PS ≥2 (OR 5.32, p=0.001) and with presence of solid organ metastasis (OR 3.47, p=0.013).

Conclusion: Assessment of FDG uptake in metastatic gastric cancer patients may provide useful information regarding prognosis. Further large confirmatory study may be necessary.

Keywords: Gastric cancer, FDG-PET/CT, Prognosis

A Retrospective Analysis of Stage IB Gastric Cancer (GC) Patients Who Had Underwent D2 Gastrectomy with or without Adjuvant Chemoradiotherapy

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Background: Because adjuvant treatment of stage IB GC patients after curative resection remains controversial, we performed this retrospective analysis based on the data obtained from patients with pathologically staged IB gastric adenocarcinoma.

Methods: The records of 1816 stage IB GC patients who were consecutively treated with D2 gastrectomy at Samsung Medical Center (Seoul, Korea) between 1995 and 2007 were retrieved from the cancer registry.

Results: T1N1 and T2N0 tumors were found in 619 and 1197 patients, respectively. At least 15 perigastric lymph nodes were removed in all patients. Adjuvant chemoradiotherapy was given to 657 patients after surgery. As of Aug 2009, there were 57 (3%) recurrent cases, yielding a 5-year recurrence-free survival (RFS) rate of 97%. Multivariate analysis revealed that only diffuse type Lauren histology was significantly associated with the risk of recurrence (HR 1.70, 95% CI 1.01-2.87, p=0.044). The administration of adjuvant chemoradiotherapy did not affect RFS.

Conclusion: Lauren classification could be used to identify the subgroup of patients most likely to benefit from adjuvant therapy for stage IB GC.

Oxaliplatin Combined with Continuous Infusion of 5-fluorouracil as First-line Chemotherapy in Patients with Metastatic or Recurrent Gastric Ade-
nocarcinoma

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Background: This clinical study was aimed to evaluate the efficacy of combination chemotherapy of oxaliplatin, leucovorin, and continuous infusion of 5-fluorouracil (5-FU) for advanced gastric cancer.

Methods: Patients with previously untreated gastric cancer with measurable disease received oxaliplatin (100 mg/m², D1), followed by leucovorin (100 mg/m², D1) and 5-FU (2,400 mg/m², D1-2), which was repeated every 2 weeks. The primary endpoint was overall response rate (ORR) and secondary endpoints were progression-free survival (PFS), overall survival (OS), and toxicity.

Results: Forty-eight patients were enrolled, and 45 were evaluable for response. A total of 320 cycles of chemotherapy were administered (median 6 cycles per patient). One complete response (2.1%) and 19 partial responses (39.6%) were noted resulting an ORR of 41.7% (95% CI: 27.7-55.6%) by intent-to-treat analysis. With a median follow-up duration of 22 months, the median PFS was 5.3 months (95% CI: 2.8-7.8) months and the median OS was 13.6 months (95% CI: 9.3-17.9) months. There was one treatment-related death, and the most common grade 3/4 toxicity was neutropenia (95% CI: 9.3-17.9) months. There was one treatment-related noneuproidemia (36.1%). Three patients discontinued treatment because of serum creatinine elevation.

Conclusion: This study reaffirms the efficacy of oxaliplatin in advanced gastric cancer but its dose of 100 mg/m² remains to be reconsidered in Korean patients.

Keywords: Gastric cancer, Chemotherapy, Oxaliplatin

P-18

Clinical Outcome of Advanced Gastric Cancer Patients with Bone Marrow Metastases

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Background: Prognosis for gastric cancer patients with bone marrow metastases is extremely poor. The current study was performed to evaluate clinical outcome of advanced gastric cancer patients with bone marrow metastases.

Methods: We retrospectively reviewed the medical records of 26 advanced gastric cancer patients with bone marrow metastases between September 1986 and February 2009 at Soonchunhyang University College of Medicine.

Results: The median age was 46 years (range 24-61 years). All patients had poorly differentiated adenocarcinoma, including 17 signet ring cell carcinomas. The majority of the patients showed thrombocytopenia, anemia, elevation of lactate dehydrogenase. 16 patients (61.5%) were received palliative chemotherapy with a median of 4 cycles per patient (range, 1-13 cycles). Median survival durations after

P-17

Clinical Outcomes and Prognostic Factors of Metastatic Gastric Carcinoma Patients Who Experience Gastrointestinal Perforation

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Background: We underwent the current study to investigate the clinical outcomes of metastatic gastric carcinoma (MGC) patients who experienced GI perforation during palliative chemotherapy, and to examine prognostic factors.

Methods: We reviewed the medical records of patients who developed GI perforation during palliative chemotherapy in the Gastric Cancer Branch of National Cancer Center, Korea between January 2001 and December 2008.

Results: Among a total of 1,856 patients who had received palliative chemotherapy from MGC, 32 patients (1.7%) developed GI perforation during chemotherapy. Most of patients (71.9%) experienced it during the 1st line chemotherapy with the median of 2.0 months following initiation of chemotherapy. The most common perforation site was primary tumor site (68.8%) followed by metastatic site (25.0%) and non-tumor site (6.3%). Fourteen patients (43.8%) could resume chemotherapy after perforation, disease control rate was 57.1%, and median overall survival (OS) after perforation was 7.5 months (95% confidence interval [CI], 6.0-9.0 months). No previous surgery, shorter duration from initial chemotherapy to perforation, lack of disease progression, no bowel involvement, and higher albumin level at perforation were associated with resumption of chemotherapy. In all patients, median OS following perforation was 4.0 months (95% CI, 1.5-6.6 months) and multivariate analysis revealed that differentiated tumor histology, response to chemotherapy before perforation, and no septic shock at perforation were significantly associated with favorable OS after perforation.

Conclusion: Since patients experiencing GI perforation during palliative chemotherapy have heterogeneous clinical setting regarding severity of clinical feature, tumor burden, chemotherapy responsiveness, and the timing of perforation in disease course, we need to adopt different approach in management of these patients according to prognostic factors.

Keywords: Gastrointestinal perforation, Gastric cancer, Chemotherapy, Prognosis

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bone marrow metastases for entire patients were 37 days (95% CI, 12.5-61.5 days). The median survival times from bone marrow involvement were 11 days in the best supportive care group (range 9.5-12.5 days) and 121 days (range 94.7-147.3 days) in the palliative chemotherapy group (p<0.001). Patients died of tumor progression (11 patients, 45%), brain hemorrhage (6 patients, 25%), infection (5 patients, 21%), and DIC (1 patient, 4%). There were no chemotherapy related deaths.

**Conclusion:** This study suggests that palliative chemotherapy should be actively considered in advanced gastric cancer patients with bone marrow metastases.

**Keyword:** Advanced gastric cancer

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**P-19**

Oxaliplatin, 5-FU, Folinic Acid as First-line Treatment in Metastatic or Recurrent Gastric Cancer

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**Background:** Oxaliplatin shows considerable activity and also has synergism with 5-fluorouracil (5-FU) in several phase II studies for treating advanced gastric cancer. We investigated the efficacy and safety of a combination of oxaliplatin, 5-FU, and folinic acid (FA) as first-line chemotherapy for patients with metastatic or recurrent gastric cancer.

**Methods:** From January 2006 to August 2009, 39 patients with histologically confirmed, metastatic or recurrent gastric cancer underwent chemotherapy, and the results were retrospectively investigated. Chemotherapy consisted of oxaliplatin 100 mg/m² and FA 200 mg/m² (2-hour infusion), and then 5-FU 2,400 mg/m² (46-hour continuous infusion) every 2 weeks.

**Results:** Total 39 patients were studied between January 2006 and August 2009. Median age of the patients was 63 years (range: 38 to 77 years), 95% (37/39) had a the Eastern Cooperative Oncology Group performance status was 0 or 1. 79% (31/39) had newly diagnosed, and 21% (8/39) had recurrent disease. All patients were assessable for toxicity and 32 of 39 patients were evaluable for response. 39 patients received a total of 210 treatment cycles. The median number of cycles was six (range: 1~16 cycles). None achieved a complete response (CR) and 11 achieved a partial response (PR), resulting in an overall response rate of 34.4%. Stable disease was observed in 14 patients (43.8%). The median time to progression (TTP) was 4.3 months (95% CI: 2.0~6.5 months) and the median overall survival (OS) was 9.8 months (95% CI: 3.5~16.0 months). The main hematologic toxicities were anemia and neutropenia, which were observed in 119 cycles (56.7%) and 100 cycles (47.6%), respectively. Grade 3/4 neutropenia was observed in 32 cycles (15.2%). 2 patients experienced febrile neutropenia. The main non-hematologic toxicities was nausea, which was observed in 88 cycles (41.9%). Peripheral neuropathy occurred in 71 cycles (33.8%), all were grade 1 or 2. No treatment related deaths were reported.

**Conclusion:** This study showed that combination chemotherapy with oxaliplatin, 5-FU and FA is well tolerated and active as first-line treatment in patients with metastatic or recurrent gastric cancer.

**Keywords:** Oxaliplatin, Gastric cancer, Chemotherapy

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**P-20**

A Phase II Study of Biweekly Chemotherapy with Irinotecan, 5-fluorouracil, and Leucovorin (FOLFIRI) in Patients with Advanced Gastric Cancer after Failure of Prior Chemotherapy Including Taxane, Fluoropyrimidine, Platinum

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**Background:** Irinotecan is one of the chemotherapeutic agents proven active in advanced gastric cancer (AGC) and also suggested synergistic with 5-fluorouracil (5-FU) in preclinical studies. We performed this study to evaluate the efficacy and toxicities of a combination of irinotecan, 5-FU, and leucovorin (LV) continuous infusion regimen (FOLFIRI) as a salvage treatment in patients with AGC after failure of prior chemotherapy including taxane, fluoropyrimidine, and platinum.

**Methods:** A total of 43 patients were enrolled in this study between October 2004 and April 2008. Treatment comprised irinotecan (150 mg/m² on day 1) as a 2-hour infusion followed by LV 100 mg/m², and 400 mg/m² of bolus plus 2,400 mg/m² of continuous infusional 5-FU over 46 hours. Cycles were repeated every 2 weeks.

**Results:** Among a total of 43 patients, 8 (18.6%; 95% CI, 6.3-31%) achieved partial response, and 18 (41.9%) showed stable disease. With a median follow-up of 11.9 months (range, 7.0-20.4 months) in surviving patients, the median progression free survival (PFS) was 4.5 months (95% CI, 3.1-5.9 months) and the median overall survival (OS) was 10.3 months (95% CI, 8.5~12.1 months). The major factor determining PFS and OS by FOLFIRI was time to progression after previous chemotherapy (TTP). The median PFS was 2.3 months (TTP<4 mo) vs. 5.9 months (TTP≥4 mo, p=0.01). The median OS was 9.6 months (TTP<4 mo) vs. 11.5 months (TTP≥4 mo, p=0.047). Grade 3/4 neutropenia was observed in 61.3%, however, neutropenic fever was rare (4.5%). Grade 3/4 nonhematologic toxicities were asthenia (9.1%), anorexia (6.8%), nausea (4.5%), and vomiting (4.5%). There was no treatment related mortality.
Conclusion: FOLFIRI was active and tolerable as a salvage regimen after failure of previous chemotherapy with taxane, fluoropyrimidines, and platinum.

Keywords: irinotecan, 5-fluorouracil, Leucovorin, FOLFIRI, Salvage chemotherapy, Advanced gastric cancer

A Phase II Study of Docetaxel and Oxaliplatin Combination as First-line Chemotherapy in Recurrent Gastric Cancer Patients after Fluoropyrimidine and/or Cisplatin Adjuvant Treatment

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Background: After two important randomised trials of the East (S-1 as adjuvant treatment) and the West (MAGIC trial), surgery alone is no longer the standard treatment for patients with resectable gastric cancer. Therefore, urgent investigation is demanded which regimen is more effective for patients with recurrent gastric cancer after combined treatment with surgery and perioperative or adjuvant chemotherapy.

Methods: Patients with histologically confirmed and measurable advanced gastric cancer that had relapsed after fluoropyrimidine and/or cisplatin-based adjuvant chemotherapy received docetaxel 35 mg/m² i.v. on day 1, 8 plus oxaliplatin 100 mg/m² i.v. on day 1 every 3 weeks until disease progression or unacceptable toxicities.

Results: Between Feb 2007 and Mar 2009, total 27 patients (pts) who had received adjuvant chemotherapy for median 5.7 months (range, 0.1-49.1) were enrolled. After a median 4 (range, 1-13; total, 123) cycles of chemotherapy, 25 pts and 120 cycles were evaluable for response and toxicity, respectively. In intention-to-treat analysis, the overall response rate was 44.0% (95% C.I., 24.6-63.4%), including 1 CR, 10 PRs. After a median follow-up of 8.5 months (range, 2.0-20.6), median time to progression was 6.9 months (95% C.I., 3.4-10.4) and median overall survival was 12.8 months (95% C.I., 8.7-16.7). Commonly observed grade 3/4 adverse events were neutropenia (52.2% of pts), diarrhea (20.0%). Treatment was delayed in 29 cycles (24.2%). The dose of docetaxel on D1, 8 and oxaliplatin were reduced during 22 (18.3%), 25 (20.8%) and 23 cycles (19.2%), respectively. Major causes for treatment delay and dose reduction of two drugs were neutropenia and diarrhea. There were three pts of neutropenic fever, and one pt of treatment-related death.

Conclusion: Docetaxel and oxaliplatin combination chemotherapy was active and tolerable except grade 3 diarrhea as first-line treatment in patients with recurrent gastric cancer after fluoropyrimidine and/or cisplatin-based adjuvant chemotherapy.

Keywords: Recurrent gastric cancer, First-line treatment, Docetaxel, Oxaliplatin

RIPK1 Gene Polymorphism as a Prognostic Marker for Survival in Patients with Colorectal Cancer

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Background: Since apoptosis plays a key role in cancer progression, the present study analyzed the polymorphisms of apoptosis-related genes and their impact on the survival after curative resection in patients with colorectal cancer.

Methods: Three hundred and ninety seven patients with colorectal cancer who underwent surgery with curative intent were enrolled in the present study. The genomic DNA was extracted from fresh colorectal mucosal tissue, and the 15 SNPs of 12 apoptosis-related genes (FAS, FAS ligand [FASLG], TNSFR1A, TNSFR10B, RIPK1, TP53, PTGS2, CASP3 and CASP6-9) were determined using a Sequenom MassARRAY system.

Results: During the median follow-up of 41.6 (range, 0.7-85.5) months, 80 relapses and 67 deaths occurred. Among the target polymorphisms, FAS rs10788624 and rs1800682 in a recessive model of the minor allele and RIPK1 rs2272990 in a dominant model of the A allele were associated with survival in a log-rank test. Moreover, the GA+AA genotype of RIPK1 +83G>A (rs2272990) was significantly correlated with a worse disease-free and disease-specific survival comparing to the GG genotype (hazard ratio [HR]=1.810; 95% confidence interval [CI]=1.108-2.959; p=0.018 and HR=2.372; 95% CI=1.302-4.321; p=0.005, respectively) in a multivariate survival analysis including age, sex, histologic grade, pathologic stage, primary tumor site, CEA level, and adjuvant chemotherapy. No clinicopathologic difference was observed according to the genotypes of these three polymorphisms.

Conclusion: RIPK1 gene polymorphism can be considered as a possible prognostic marker for survival after curative resection in patient with colorectal cancer.

Keywords: RIPK1, Polymorphism, Prognosis, Colorectal cancer
Prognostic Impact of MicroRNA-related Gene Polymorphisms on Survival of Patients with Colorectal Cancer

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Background: The polymorphisms in microRNA (miRNA) machinery genes and miRNA-containing genomic regions may play an important role in cancer development and prognosis. Accordingly, the present study analyzed the single nucleotide polymorphisms (SNPs) of miRNA-related genes and their impact on the prognosis for patients with colorectal cancer.

Patients and Methods: Four hundred and twenty-six consecutive patients with surgically treated colorectal adenocarcinoma were enrolled. The genomic DNA was extracted from fresh colorectal tissue and 40 polymorphisms of DNA repair genes determined using a real-time PCR genotyping assay.

Methods: Four hundred and twenty-six consecutive patients with surgically treated colorectal adenocarcinoma were enrolled. The genomic DNA was extracted from fresh colorectal tissue and 40 polymorphisms of DNA repair genes determined using a real-time PCR genotyping assay.

Results: In a univariate analysis, the progression-free survival (PFS) of the patients with the combined mir492 C/G and G/G genotype was significantly worse than that of the patients with the mir492 C/C genotype (rs2289030) (p value=0.0426), although there was no difference in the overall survival (PFS) of the patients with the combined mir492 C/G and G/G genotype was significantly worse than that of the patients with the mir492 C/C genotype (rs2289030) (p value=0.0426), although there was no difference in the overall survival. In a multivariate analysis, the progression-free survival of the patients with the combined mir492 C/G and G/G genotype was significantly worse than that of the patients with the mir492 C/C genotype (rs2289030) (p value=0.0426), although there was no difference in the overall survival. In a multivariate analysis, the progression-free survival of the patients with the combined mir492 C/G and G/G genotype was significantly worse than that of the patients with the mir492 C/G and G/G genotype was significantly worse than that of the patients with the mir492 C/C genotype (rs2289030) (p value=0.0426), although there was no difference in the overall survival. In a multivariate analysis, the progression-free survival of the patients with the combined mir492 C/G and G/G genotype was significantly worse than that of the patients with the mir492 C/C genotype (rs2289030) (p value=0.0426), although there was no difference in the overall survival.

Conclusion: None of the 40 miRNA-related gene polymorphisms investigated in this study was found to be an independent prognostic marker for Korean patients with surgically resected colorectal cancer. However, further studies are warranted to clarify the role of miRNA-related gene polymorphisms as a prognostic biomarker for colorectal cancer patients.

Keywords: Colorectal cancer, miRNA, Polymorphism, Prognosis

Randomized Phase III Trial Comparing Preoperative versus Postoperative Radiotherapy with Capecitabine in Locally Advanced Rectal Cancer

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Background: Preoperative chemoradiotherapy using bolus fluorouracil demonstrated the superiority of preoperative treatment over postoperative treatment in local control and sphincter preservation in locally advanced rectal cancer. We conducted a prospective, single-institutional, phase III trial which compared preoperative chemoradiotherapy with postoperative chemoradiotherapy using oral capecitabine. We present the final results of our trial in this report.

Methods: Patients with locally advanced rectal cancer (cT3 or N+) were randomly assigned to receive either preoperative (arm I) or postoperative (arm II) chemoradiotherapy. Preoperative radiotherapy was delivered to the pelvis at a dose of 46 Gy in 23 fractions, followed by a boost of 4 Gy in 2 fractions. Postoperative radiotherapy consisted of 50 Gy in 25 fractions to the pelvis without boost. Capecitabine (1,650 mg/m2/day) was administered concurrently during radiotherapy. Surgery was performed according to total mesorectal excision technique with the time interval of 4-6 weeks in both arms. This protocol was closed earlier than initially planned due to difficulty in patient enrollment.

Results: Between March 2004 and April 2006, 117 and 123 patients were randomly assigned to arm I and arm II, respectively. Clinical characteristics were well balanced between the two arms, except more low-lying (≤5 cm from anal verge) tumors in arm I (60% vs. 46%, p=0.041). After a median follow-up of 47 months, the 5-year cumulative incidence local recurrence was non-significantly higher in arm II (3% vs. 6%, p=0.335). The 5-year overall survival and disease-free survival rates were not different between two groups. In the patients with lower-lying tumors, arm I showed higher rate of sphincter sparing surgery (68% vs. 42%, p=0.008). Ninety-nine patients (92.5%) in arm I and 84 patients (74.3%) in arm II completed chemoradiotherapy as planned. Grade 3 or higher acute toxicity was observed in 15% of the patients in arm I and 84 patients (74.3%) in arm II completed chemoradiotherapy as planned. Grade 3 or higher acute toxicity was observed in 15% of the patients in arm I and 84 patients (74.3%) in arm II completed chemoradiotherapy as planned. Grade 3 or higher acute toxicity was observed in 15% of the patients in arm I and 84 patients (74.3%) in arm II completed chemoradiotherapy as planned. Grade 3 or higher acute toxicity was observed in 15% of the patients in arm I and 84 patients (74.3%) in arm II completed chemoradiotherapy as planned.

Conclusion: Preoperative or postoperative chemoradiotherapy with oral capecitabine was safe and well tolerated. Although we could not demonstrate significant benefit of preoperative chemoradiation in local control and survival, our data showed that increased rate of sphincter preservation was possible in lower-lying tumors without jeopardizing local control and surgical complication by preoperative chemoradiation therapy.

Keywords: Rectal cancer, Preoperative chemoradiotherapy, Capecitabine, Randomized controlled trial
A Pilot Study of Neoadjuvant Chemoradiation with Higher Dose Enteric-coated Tegafur/Uracil Plus Leucovorin for Locally Advanced Rectal Cancer

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Background: Neoadjuvant chemoradiation (CRT) with tegafur/uracil (UFT) 200-350 mg/m²/day plus leucovorin (LV) 25-75 mg/day for 5 days a week with 45 Gy radiation (RT) for locally advanced rectal cancer (LARC) was known to be efficacious and tolerable, but higher dose UFT/LV and RT may improve pathologic response rate. We have performed a pilot study to evaluate pathologic response rate and toxicity profile of neoadjuvant CRT with higher dose enteric-coated tegafur-uracil (UFT-E)/LV.

Methods: Patients (pts) were planned to be treated with UFT-E 400 mg/m²/day plus LV 90 mg/day for 7 days a week during RT 50.4 Gy. Main eligibility criteria were histologically proven rectal adenocarcinoma; T2-4 lesions; age > 18 years; ECOG PS 0-1; no prior chemotherapy or pelvic irradiation. Total mesorectal excision was planned to be performed 4-8 weeks after completion of CRT.

Results: Between June 2008 to January 2009, 39 pts were enrolled; median age 57 years (40-92); M/F 26/13; PS 0/1; 27/13; cT2/T3 2/3; N0/N+ 6/29; median tumor location from anal verge 6.0 cm (2.0-9.0). The median relative dose intensity of UFT-E was 95.0% (51.6-111.7). Three pts were given reduced dose RT (1 with 27 Gy, 2 with 45 Gy) due to grade 3/4 diarrhea; 5 pts needed UFT-E dose interruption due to toxicities. Grade 3/4 toxicities included leukopenia (2, 5.1%), neutropenia (3, 7.7%), hyperglycemia (4, 10.3%), elevated transaminase level (2, 5.1%), diarrhea (4, 10.3%), nausea (2, 5.1%), and pain (2, 5.1%). Of 36 pts who underwent surgery (all R0 resection), 22 (61.1%) were treated with sphincter saving procedure. Pathologic T0 and N0 were observed in 8 (22.2%) and 29 (80.6%) pts, respectively. Downstaging in T stage was achieved in 24 pts (66.6%). Pathologic complete responses were observed in 8 (22.2%) pts and another 7 (19.4%) pts had only minimal microscopic residual tumor.

Conclusion: Neoadjuvant CRT with higher dose UFT-E/LV showed favorable efficacy and tolerability. A phase II trial of CRT with higher dose UFT-E/LV is ongoing.

Keywords: Rectal cancer, Preoperative chemoradiotherapy, UFT-E

Brain Metastases from Colorectal Carcinoma: Prognostic Factors and Outcome

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Background: Brain metastases from colorectal carcinoma (BRM) are increasing as a result of advancements in treatment of colorectal cancer. Prognostic factors and overall survival (OS) for BRM are important clinical information. The purpose of this study was to investigate prognostic factors and OS in patients with BRM.

Methods: Baseline characteristics, treatment modality, and outcome of patients with BRM were collected from the medical records of Yonsei Cancer Center and analyzed over a 5 year period (2005-2010). A total of 62 patients were included in the analysis. Prognostic factors were analyzed using Cox proportional hazards model.

Results: Median OS was 11.0 months. Multivariate analysis revealed that Eastern Cooperative Oncology Group (ECOG) performance status (PS), number of brain metastases, number of systemic metastases, and presence of extra cranial metastases were independent prognostic factors of poor survival. Median OS was 10.0 months for patients with ECOG PS 0-1 and 4.5 months for those with ECOG PS 2. Median OS was 12.6 months for patients with 1 or 2 brain metastases, and 9.3 months for those with 3 or more brain metastases. Median OS was 21.0 months for patients with 0 systemic metastases and 9.7 months for those with 1 or more systemic metastases. Median OS was 11.0 months for patients with extra cranial metastases and 8.9 months for those without extra cranial metastases.

Conclusion: ECOG PS, number of brain metastases, number of systemic metastases, and presence of extra cranial metastases were independent prognostic factors of poor survival in patients with BRM. These factors can be used to predict survival and guide treatment decisions.
Background: Brain metastases from colorectal carcinoma are rare. The objectives of the current study were to assess the natural history, outcome, and possible prognostic factors in colorectal cancer patients with brain metastasis.

Methods: Between 1995 and 2008, 8732 patients with colorectal carcinoma were treated at Yonsei University Health System. Of those, 126 (1.4%) had a diagnosis of brain metastasis. We carried out a retrospective review of these 126 patients and performed a statistical analysis.

Results: The median age at the time patients were diagnosed with brain metastasis was 62 years (range, 29-90) and 81 patients (62.3%) were male. Median time from diagnosis of colorectal carcinoma to brain metastasis was 22.7 months (range, 0-139), and 13 patients (10.3%) had brain involvement as their initial presentation. The most common presenting symptoms were headache and motor weakness. Metastases were treated with whole-brain radiation therapy (WBRT) alone in 45 patients (35.7%) and gamma knife surgery (GKS) alone in 41 patients (32.5%). 14 patients (11.1%) underwent surgical resection followed by WBRT. Twenty patients (15.9%) received steroids only. Median follow up duration was 6.1 months (range, 0.1-90.3) and median survival after diagnosis of brain metastasis was 5.4 months (95% CI, 3.9-6.9). The median survival time after the diagnosis of brain metastasis was 1.5 months for patients who received only steroids, 4.0 months for those who received WBRT, 9.5 months for those who received GKS, and 11.5 months for those who underwent surgery (p<0.001). Univariate analysis showed that treatment modality, number of brain lesions, Kornofsky performance score (KPS), recursive partitioning analysis (RPA) class, interval from diagnosis of primary tumor to brain metastasis, treatment response for brain and systemic metastasis and whether received chemotherapy after brain metastasis had a statistically significant impact on survival. In multivariate analysis, treatment modality, KPS, interval from diagnosis of primary tumor to brain metastasis, treatment response for brain and systemic metastasis and whether received chemotherapy after brain metastasis were statistically significant prognostic factors for survival.

Conclusion: The overall prognosis of patients with brain metastases from colorectal carcinoma was poor. Nevertheless, some subsets of patients manifested the most favorable survival criteria (good performance scale and treatment response); thus, for at least these patients, treatment may result in an improved survival time.

Keywords: Brain metastasis, Colorectal carcinoma, Prognostic factor

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Mitomycin-C, 5-fluorouracil and Leucovorin as a Salvage Therapy in Patients with Metastatic Colorectal Adenocarcinoma: A Retrospective Analysis

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Background: With the recent development of 5-fluorouracil (5-FU)-based chemotherapy in combination with the targeted agents (cetuximab, bevacizumab), the prognosis of patients with metastatic colorectal patients has been improved. However, active anticancer drugs and/or combination regimens for the treatment of patients failing oxaliplatin, irinotecan and 5-FU are desperately needed. In this analysis we describe the safety and efficacy of the combination of mitomycin C, 5-FU and leucovorin in such an extensively pretreated patient population.

Methods: Between March 2008 and September 2009, a total of 40 patients were treated with mitomycin C (10 mg/m² on day 1) and leucovorin 20 mg/m²/day (2-h intravenous infusion) followed by 5-fluorouracil 1,200 mg/m²/day (for 22-h continuous intravenous infusion) every 2 weeks. All patients had failed prior first-line and second-line treatment with oxaliplatin, irinotecan and 5-fluorouracil. The aim of this retrospective analysis was to evaluate the efficacy and safety data of this potential salvage therapy regimen.

Results: The overall response rate (intent-to-treat) was 2.5% and disease stabilization was achieved in 40%. Median time to progression was 10.3 weeks (95% Confidence interval; 8.4-12.2) and median overall survival was 40 weeks (95% Confidence interval; 32.7-47.3). Myelosuppression was the most frequent side effect. Grade 3 and 4 hematologic toxicities included neutropenia in 5 patients (12.5%) and thrombocytopenia in 3 patients (7.5%). The most common nonhematological toxicities consisted of mild vomiting in 2 patients (5%). Grade 1 or 2 peripheral neuropathy was observed in 5 patients (12.5%). One treatment related thromboembolism and two Hemolytic-uremic syndrome patients were observed.

Conclusion: These data show that the combination of mitomycin C/5-FU/leucovorin is safe and active in about 40% of patients in terms of abrogation of progression in extensively pretreated metastatic colorectal cancer.

Keywords: Colorectal cancer, Mitomycin C, Salvage therapy

The Effect of DNA Mismatch Repair (MMR) Status on Oxaliplatin-based First-line Chemotherapy as in Recurrent or Metastatic Colon Cancer

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Background: Colon cancer with DNA mismatch repair (MMR) defects reveals distinct clinical and pathologic features, including a better prognosis and reduced response to 5-fluorouracil (5-FU)-based chemotherapy. A current treatment of reference for recurrent or metastatic colon cancer uses capcitabine plus oxaliplatin (CAPOX), or continuous-infusion fluorouracil plus oxaliplatin (FOLFOX). This study investigated the effect of MMR status on the treatment outcomes for CAPOX and FOLFOX as first-line combination chemotherapy in recurrent or metastatic colon cancer.

Methods: We analyzed 171 patients who had been treated with XELOX or FOLFOX as first-line combination chemotherapy in recurrent or metastatic colon adenocarcinoma between February 2004 and July 2008. Tumor expression of the MMR proteins, MLH1 and MSH2, was detected by immunohistochemistry (IHC) in surgically resected tumor specimens. MSI was analyzed by polymerase chain reaction (PCR) amplification, using fluorescent dye-labeled primers specific to microsatellite loci. Tumors with MMR defect were defined as those demonstrating a loss of MMR protein expression (MMR-D) and/or a microsatellite instability-high (MSI-H) genotype.

Results: In all, 75 patients (44%) received FOLFOX and 96 patients (56%) received CAPOX as first-line combination chemotherapy. The incidence of colon cancer with MMR defect was 10/171 (6%). Colon cancers with MMR defect (MSI-H and/or MMR-D) are more commonly located in proximal to the splenic flexure (p=0.03). The MMR status did not significantly influence the overall response (p=0.95) to first-line CAPOX or FOLFOX treatment in recurrent or metastatic colon cancer patients. According to the MMR status, there was no significant difference for PFS (p=0.50) and OS (p=0.47) in recurrent or metastatic colon cancer patients treated with first-line CAPOX or FOLFOX. In colon cancers with MMR-defect, there was no significant difference for PFS (p=0.48) and OS (p=0.56) between CAPOX and FOLFOX as 1st line combination chemotherapy. However, in MMR intact, there was significant difference for OS between CAPOX and FOLFOX (p=0.04). OS was significant better in patients treated with CAPOX as compared to patients with FOLFOX.

Conclusion: The MMR status does not predict the effect of oxaliplatin based combination chemotherapy as 1st line in recurrent or metastatic colon cancers. CAPOX in the 1st line treatment of recurrent or metastatic colon cancer with MMR intacts showed a superior OS compared with FOLFOX unlike colon cancer with MMR defects.

Keywords: MMR, MSI, CAPOX and FOLFOX

Comparison of Survival Difference according to T Stage between the Current (6th) and the Proposed (7th) TNM Staging System in Non-Small Cell Lung Cancer (a Single Center Experience)

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Background: Recently, the seventh version of the TNM staging system was proposed for non-small cell lung cancer (NSCLC). However, the current (6th) version of TNM staging system is still used widely. We investigated the differences between the current and the proposed staging system by the primary tumor characteristics (T), one of the descriptor of TMN staging system.

Methods: We found 393 patients with a diagnosis of NSCLC with stage of pT1-4N0M0 from Dec. 1997 to Dec. 2002 in our institution’s registry (minimum follow up duration of survivors >6 years). All patients had initially undertaken R0 surgical treatment and mediastinal lymph node dissection. All survivors were followed up to June 2009.

Results: Both the current T staging system and the proposed T staging system showed a statistical significance in discriminating the patient’s overall survival according to the stage of T (p<0.01). In 95 patients who had T1N0M0 in the current (6th) staging system, 38 patients were classified to T1a in the proposed (7th) staging system, and 57 patients to T1b. There was no statistically significant difference in OS rates (p=0.775). In 242 patients who had T2N0M0 in the current (6th) staging system, 188 patients classified to T2a in the proposed (7th) staging system, 33 patients to T2b and 21 patients to T3. In this current (6th) T2 stage, there was a significant difference in patient’s OS rate according to the sub-divided T stage of the proposed (7th) staging system (p<0.01). The median OS did not reach in the patients classified to T2a in the proposed (7th) staging system until 132-month follow-up (5-year OS rate: 71.4%); however, the median OS was 43.7 months in the patients who classified to T2b (5-year OS rate: 48.5%) and 56.6 months in the patients who classified to T3 (5-year OS rate: 47.6%). In the patients classified to T2a in the proposed (7th) staging system, the 5-year OS rate was higher in the patients classified due to atelectasis/obstructive pneumonitis only than in patients classified due to size or invasion of visceral pleura (86.2% vs. 67.7% or 76.9%). All forty-four patients, who had T3N0M0 stage in the current (6th) staging system, still showed T3 in the proposed (7th) staging system. The me-
dian OS was 41.7 months. In 12 patients who had T4N0M0 in the current (6th) staging system, there were seven patients who showed down-staged T3 according to the proposed (7th) staging system, and only five patients still had T4 in the proposed (7th) staging system.

Conclusion: The proposed 7th staging system has some changes from the current 6th staging system. When our cohorts with the current T2N0M0 were subdivided according to the primary tumor size, there was a survival difference, especially by the size criterion of 5 cm. The subgroup of proposed T2aN0M0 by atelectasis/obstructive pneumonitis only criterion showed better survival than the other patients in the same group.

Keywords: Non-small cell lung cancer, TNM staging system

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Results of Conventional Definitive 3D-CRT alone for Non-small Cell Lung Cancer

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Background: Definitive treatment of choice in non-small cell lung cancer (NSCLC) is a surgery for resectable tumor or combined chemoradiotherapy for unresectable tumor. But co-morbid medical problem can disturb the definitive treatment in some patients. Most report of RT alone for NSCLC was out of date with 2-dimensional treatment and relatively low radiation dose, 60 Gy or below. In this report, the results of 3-dimensional conformal radiotherapy (3D-CRT) with curative intent in 41 patients are presented.

Methods: One hundred and fifty NSCLC patients treated with 3-dimensional (3D) definitive conventional radiotherapy alone from JAN 2002 to DEC 2007 were recruited to this retrospective study. Among them, 74 patients excluded in the analysis because of low radiation dose, double primary, follow-up loss after treatment and 41 patients were analyzed. Median age was 74 years and most patients were male. Two-thirds patients had squamous cell carcinoma (SCC) and clinical stage was IB (10%), II (54%), III (36%). The causes of radiotherapy alone were old age, poor lung function or co-morbid medical problems. Two times of CT simulation was done in all patients at start and after two-thirds of treatment course. Radiotherapy dose was 66 Gy in 30 fractions, as fractionation size was 2.2 Gy per day. Primary mass and involved hilar or mediastinal nodal stations were included, but elective nodal irradiation was not done. Tumor response was evaluated from chest CT 1 months after completion of radiotherapy using uni-dimensional RECIST criteria. Survival was estimated from the date of radiotherapy start and Kaplan-Meier method was used.

Results: Tumor response 1 month after radiotherapy was judged to major response in 22 (53%), stable disease in 18 (44%) and disease progression in 1 (3%) patients. During the follow-up period, 22 patients suffered from disease recurrence and the first failure site was locoregional recur in 17, distant metastasis in 5 and both in 6 patients. Median follow-up period was 15 months. Median survival time was 15 months and 2 year overall survival rate was 37%. Among the 30 deaths, 20 died of lung cancer. Locoregional progression occurred in 17 patients and 2 year locoregional progression-free survival was 44. Tumor size was only the signifiant factor for overall survival in both univariate and multivariate analysis. Radiation esophagitis and pneumonitis were major treatment-related complications. No G3 or above radiation esophagitis was noted, but two patients suffered from G3 radiation pneumonitis. No treatment-related death was revealed.

Conclusion: Treatment results with RT alone was not so disappointing although most patients have medical problems. 3D-CRT with 66 Gy/30 fractions, 2.2 Gy per fraction made no major problem in most patients. But local tumor progression was a major failure pattern despite RT alone. So the escalation of radiation dose above 66 Gy/30 fractions is needed in the 3D-CRT alone for the effective locoregional tumor control. We are supposed to promote the dose escalation study for 3D-CRT alone in non-metastatic NSCLC.

Keywords: Non-small cell lung cancer, Radiotherapy alone, 3-dimensional, Outcome

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An Association of the Age at Diagnosis with the Presence of EGFR Mutations in Female Patients with NSCLC: A Single-Institution Retrospective Analysis

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Background: Our previous report showed associations between age and outcome in gefitinib-treated female patients with non-small cell lung cancer (NSCLC). However, there are rare molecular studies in respect to presence of epidermal growth factor receptor (EGFR) mutations according to age. This retrospective study was performed to evaluate a possible association between age at diagnosis and the presence of EGFR mutations in female patients with NSCLC.

Methods: Tissue samples were obtained from specimens of 99 female patients with primary NSCLC subjected to curative surgical resection from January 1992 to December 2002 at the Korea Cancer Center Hospital. The EGFR Scorpions kit was used to detect mutations.

Results: Most of the study population comprised never-smokers (82%) and patients with adenocarcinoma (81%).
The age at diagnosis ranged from 34 to 74 (median 57.2). When a median age was used as a cut off value, old patients were more likely to have EGFR mutations than young (69.4% versus 40.0%; p=0.005). After controlling effects of histology, smoking history, and stage, the old age remained a significant predictors for EGFR mutations (hazard ratio, 4.686; p=0.001). We observed that age at diagnosis was associated with the presence of EGFR mutation, a molecular evidence for our previous study.

**Conclusion:** Our data suggest that age might be helpful to discriminate patients who harbor EGFR mutations, strong indicators for favorable outcomes.

**Keywords:** Non-small cell lung cancer, EGFR mutation, Female, Age

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**A Phase II Study of Combination Chemotherapy with Docetaxel and Carboplatin for Elderly Patients with Advanced Non-small Cell Lung Cancer**

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**Background:** More than 50% of all advanced non-small cell lung cancer (NSCLC) is diagnosed in patients older than 65 years. Chemotherapy in elderly patients has not been standardized even though cisplatin-based chemotherapy has been used in patients with advanced NSCLC as primary therapy. We investigated the efficacy and safety of combination chemotherapy with docetaxel and carboplatin for elderly patients with advanced NSCLC.

**Methods:** Chemotherapy-naïve patients (age ≥65 years) with stage IIIb or IV NSCLC were enrolled. Patients received docetaxel (75 mg/m^2 on D1) and carboplatin (AUC of 5 mg/ml/min on D1) every 3 weeks. The end points included the response rate, progression-free survival (PFS), overall survival (OS) and toxicity.

**Results:** A total of 43 patients was enrolled between March 2005 and December 2008, and 38 patients were evaluable. The median age was 74 years old (range, 65-84 years) and 39 patients (90.6%) had an ECOG PS of 0 or 1. Squamous cell carcinoma was observed in 18 patients (41.8%) and 24 patients (55.8%) had an increased Charlson comorbidity index score (CCI≥1). The median number of treatment cycles was five (range, 1-8) and the relative dose intensity was 90.4% for docetaxel and 92.7% for carboplatin. The overall response rate was 46.5% (95% CI, 31.6-61.4) for the intent-to-treat population with 1 complete response and 19 partial responses. The median follow-up duration was 14.4 months. The median PFS was 6.9 months (95% CI 6.25-7.55) and the median OS was 13.1 months (95% CI 10.20-16.07). The 1-year survival rate was 60%. In grade 3 or 4 hematological toxicities, neutropenia (37.2%), anemia (18.6%) and thrombocytopenia (4.6%) were shown. The non-hematological toxicities were tolerable.

**Conclusion:** The combination chemotherapy with docetaxel and carboplatin was effective with tolerable toxicities in elderly patients with advanced non-small cell lung cancer.

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**Elevated Serum C-reactive Protein as a Prognostic Marker in Small Cell Lung Cancer**

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**Background:** An elevated C-reactive protein (CRP) level is associated with poor prognosis in several malignancies including esophageal cancer, hepatocellular carcinoma, colorectal cancer, and renal cell cancer. The purpose of this study was to investigate serum CRP as a prognostic marker in small cell lung cancer (SCLC).

**Methods:** The pretreatment CRP level (normal, ≤0.8 mg/dl) was measured in 157 newly diagnosed SCLC patients. The correlation between serum CRP level and other clinical markers was analyzed by Pearson correlation coefficient. Univariate analyses were conducted using Kaplan-Meier survival curve and log-rank test. Multivariate analyses were performed to find prognostic markers using Cox’s proportional hazards model.

**Results:** Patients and disease characteristics included the followings: median age, 65 years (range, 46-82 years); male sex (n=140, 89.2%); extensive disease (n=98, 62.4%); weight loss (n=29, 18.5%); Eastern Cooperative Oncology Group performance status 0-1 (n=124, 79%); and responder to chemotherapy (n=104, 66.3%). The initial CRP concentration was within the normal range (0.0-0.8 mg/dl) in 72 (45.9%) patients and elevated in 85 (54.1%) patients. The mean values of CRP were 0.3±0.2 mg/dl (range, 0.1-0.8 mg/dl) in the normal CRP group and 8.4±8.8 mg/dl (range, 0.9-40.5 mg/dl) in the high CRP group. There was a significant correlation between CRP level and the extent of disease (p<0.001) or weight loss (p=0.026). Median overall survival in the normal CRP group was significantly longer compared with the high CRP group (22.5 months vs. 11.2 months, respectively, p<0.001). Extent of disease (p<0.001), age (p=0.026), performance status (p<0.001), and chemo-responsiveness (p<0.001) were additional prognostic factors on univariate analysis. On the multivariate analysis, elevated CRP level was an independent prognostic factor for poor survival (HR=1.8, 95% CI, 1.1-3.0; p=0.017), regardless of the extent of the disease (HR=2.5; p=0.001), performance status (HR=2.1; p=0.002), and che-
Conclusion: High level of CRP was an independent poor prognostic factor receptor (EGFR) gene in resected non-small cell lung cancer (NSCLC) patients receiving adjuvant chemotherapy.

Methods: The study population was composed of 156 patients who had undergone surgery for clinically operable NSCLC between January 2003 and December 2008. The patients received adjuvant chemotherapy, consisting of 4 cycles of tri-weekly paclitaxel (175 mg/m²) and carboplatin. Biologic meaning of EGFR copy number gain is not well defined yet, so the underlying mechanism of these phenomena mandates further research.

Keywords: Non-small cell lung cancer, EGFR, Copy number change

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Randomized Phase II Trial of Pemetrexed versus Gefitinib in Previously Treated Non-small Cell Lung Cancer: Preliminary Results

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Background: INTEREST study established non-inferior survival of gefitinib compared with docetaxel for pretreated patients with advanced non-small cell lung cancer (NSCLC). Each of pemetrexed and gefitinib has clinical benefits for patients with advanced NSCLC previously treated with chemotherapy. However, there is no data which drug is superior benefits. This randomized phase II trial is to compare the efficacy and safety of pemetrexed versus gefitinib in patients with previously treated locally advanced or metastatic NSCLC.

Methods: Eligible patients had a performance status 0 to 2, previous treatment with one prior chemotherapy regimen for advanced non-small cell lung cancer, and adequate organ function. Patients received pemetrexed 500 mg/m² intravenously day 1 with vitamin B12, folic acid and dexamethasone every 3 weeks or gefitinib 250 mg per day orally. The primary end point was progression free survival.

Results: Thirty-five patients were randomly assigned. One of 17 patients in pemetrexed group and 2 of 18 in gefitinib had partial response. Disease control rates are 41% (7/17) and 33% (6/18) respectively. Median progression free survival was 4.1 versus 1.7 months (p=0.62). Median survival time was 9.8 months for pemetrexed group and not reached for gefitinib (p=0.91). One patient was died due to ILD like lung disease in gefitinib group. Other toxicity was mild and tolerable in both. The most common adverse
events were anorexia (53% vs 69%) and fatigue (53% vs 43%) for pemetrexed versus gefitinib, respectively. Rash or acne (23% vs 13%) was more in gefitinib.

**Conclusion:** This preliminary results showed that treatment with gefitinib could have clinically equivalent efficacy compared with pemetrexed in the pretreated patients with advanced NSCLC. Each regimen had manageable toxicity. The accrual is ongoing.

**Keywords:** Pemetrexed, Gefitinib, Non-small cell lung cancer

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**Irinotecan Plus Carboplatin in Patients with Extensive-disease Small Cell Lung Cancer**

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**Background:** To evaluate the efficacy and safety of irinotecan in combination with carboplatin in previously untreated, extensive-disease small cell lung cancer (ED-SCLC).

**Methods:** Patients with histologically or cytologically confirmed ED-SCLC received irinotecan 60 mg/m² on days 1, 8 and 15 plus carboplatin AUC 5 on day 1 every 4 weeks. Treatment was repeated until disease progression, unacceptable toxicity or for up to 6 cycles.

**Results:** Forty-four patients were enrolled. Thirty-nine (89%) patients were male and the median age was 66 years. ECOG performance status was 0-1 in 27 (61%) patients and 2 in 17 (39%) patients. In an intent-to-treat analysis, the overall response rate was 75% (8 CR, 25 PR). With a median follow-up duration of 26.2 months, the median progression-free and overall survival were 5.6 months (95% confidence interval (CI): 4.5-6.7 months) and 8.7 months (95% CI: 6.9-10.5 months), respectively. In total, 163 chemotherapy cycles were given with a median number of four. The principle toxicities were neutropenia and diarrhea. Grade 3 to 4 neutropenia occurred in 30% of patients and three (7%) of them presented febrile neutropenia. Grade 3 to 4 diarrhea observed in 21% of patients. Three possible treatment-related deaths were observed (septic shock, pneumonia and cerebral infarction).

**Conclusion:** The combination chemotherapy of irinotecan and carboplatin is active and tolerable in patients with ED-SCLC.

**Keywords:** Irinotecan, Carboplatin, Small cell lung cancer

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**P-38**

**Interstitial Pneumonitis after Treatment with Pemetrexed for Non-small Cell Lung Cancer**

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Pemetrexed is an antifolate antineoplastic agent that exerts its action by disrupting folate-dependent metabolism. It is approved as a single agent for second-line treatment of advanced non-squamous non-small-cell lung cancer (NSCLC) with favorable toxicity profile and in combination with cisplatin for first-line therapy of advanced non-squamous non-small-cell lung cancer. We report a case of interstitial pneumonitis occurring after the second-line treatment with pemetrexed in a patient with advanced NSCLC.

The patient was a 69-year-old man with NSCLC, smoker, with adenocarcinoma of the right lung in stage IV (cT3N3M1 for metastases of the left lung and bone). After six cycles first-line chemotherapy including gemcitabine (1,000 mg/m² days 1 and 8) and carboplatin (AUC 5.5 day 1) every three weeks, he received a second-line treatment with pemetrexed (500 mg/m² day 1 every 3 weeks) with vitamin B12 and folate supplementation and steroid pre-medication. After one week, the patient developed dyspnea. After 3 weeks, he visited outpatient clinic for a second cycle of pemetrexed therapy and chest radiograph showed interstitial infiltrations at both lungs. The computed tomographic scan revealed diffuse ground glass opacity and reticulations at both lungs. We performed bronchoscopy to exclude infectious cause and VATS biopsy showed interstitial pneumonitis consistent with organizing pneumonia. Pemetrexed induced interstitial pneumonitis was diagnosed based on pathology and medical history. After high-dose steroid therapy, clinical symptom, hypoxemia and interstitial infiltration on chest X-ray were improved.

To our knowledge, this is the first report on interstitial pneumonitis following administration of pemetrexed in Korea.

**Keywords:** Pemetrexed, Interstitial pneumonitis, Non-small-cell lung cancer

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**Asymptomatic Pulmonary Embolism in Lung Cancer Patients: The Impact on Survival and the Significance of Anticoagulation Therapy**

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Asymptomatic Pulmonary Embolism in Lung Cancer Patients: The Impact on Survival and the Significance of Anticoagulation Therapy

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Background: Many pulmonary emboli are detected incidentally in lung cancer patients. However, the clinical relevance of anticoagulation therapy for asymptomatic pulmonary embolism (PE) is unknown. The purpose of our study was to retrospectively evaluate the role of the anticoagulation therapy for asymptomatic PE in lung cancer patients. We also aimed to evaluate risk factors associated with the development of PE as well as the prognostic power of PE in lung cancer patients.

Methods: The Samsung Medical Information System was used to evaluate predictors and prognosis of PE in lung cancer patients. We found patients with PE using the Radiation Interpretation Registry and reviewed their medical records.

Results: Among 8,014 lung cancer patients, the cumulative incidence rate of PE was 2.2%. Metastasis and prior history of chemotherapy were significant predictors of the development of PE. Pulmonary embolism detected within 3 months after diagnosis of lung cancer was a significant poor prognostic factor (hazard ratio [HR], 1.5; 95% CI, 1.1 to 2.0). One hundred thirteen (63%) out of 180 PE patients were incidentally found to have pulmonary embolism. Among the 113 asymptomatic PE patients, 62 patients (55%) did not receive anticoagulation therapy. In multivariate analysis, these untreated asymptomatic PE patients died sooner than those who received anticoagulation therapy for asymptomatic PE (HR, 4.1; 95% CI, 2.3 to 7.6).

Conclusion: Anticoagulation therapy for asymptomatic PE is associated with increased overall survival in lung cancer patients.

Keywords: Pulmonary embolism, Anticoagulation, Lung cancer, Incidence, Outcome

Phase II Study of a Biweekly Schedule of Docetaxel and Cisplatin in Patients with Metastatic Non-small Cell Lung Cancer

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Background: We investigated the efficacy and toxicity of a biweekly schedule of docetaxel and cisplatin in patients with metastatic non-small cell lung cancer (NSCLC).

Methods: In this study, 48 patients with previously untreated metastatic NSCLC were given combination chemotherapy consisting of docetaxel 40 mg/m² and cisplatin 40 mg/m²; both drugs were given biweekly, on days 1 and 15, every 4 weeks.

Results: A partial response and stable disease were observed in 25 patients (52.1%, 95% CI: 38.7-66.9%) and ten patients (20.8%), respectively. The overall median survival was 14.0 months (95% CI: 7.10-20.9 months). There was no treatment-related mortality. The major toxicity was grade 2 asthenia (35.4%). Grade 4 neutropenia was observed in two patients (4.2%), as was grade 3 infection (4.2%).

Conclusion: As a front-line chemotherapy in an outpatient setting for patients with metastatic NSCLC, the biweekly schedule of docetaxel and cisplatin showed effective antitumor activity with a marked reduction in hematologic toxicity, comparable to the results of previous studies using 3 week or weekly schedules. Further randomized studies are needed before this can be accepted as a standard schedule.

Keywords: Docetaxel, Cisplatin, Non small cell lung cancer, Biweekly administration

Comparison of Erlotinib (Tarceva™) versus Gefitinib (Iressa™) as the Second Line Therapy for the Treatment of Advanced Non-Small Cell Lung Cancer Patients: A Randomized Phase II Trial

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Background: A single-center, randomized, phase II trial of gefitinib versus erlotinib as the second-line therapy for advanced non-small cell lung cancer patients was performed to compare the efficacy and toxicity between two groups.

Methods: Patients with histologically or cytologically confirmed stage IIIB or IV NSCLC including recurrent or metastatic disease, with performance status from 0 to 2, were eligible if they had failed or were intolerable to first-line chemotherapy. Patients had at least two factors among three (female or non-smoker or adenocarcinoma). Enrolled patients were treated with erlotinib 150 mg daily or gefitinib 250 mg daily after randomization until disease progression or development of intolerable toxicity.

Results: A total of 96 patients were enrolled between August 2007 and October 2008. Each forty-eight patients (50%) were randomized to each group. Median age of all patients was 59 years (range, 32-83) and 82 patients (85.4%) were female. Most patients (85.4%) had ECOG PS1. Ninety patients (93.7%) were never-smoker. The clinical characteristics were well balanced between two groups. The overall response rate of gefitinib group was 47.9% (95% CI, 33.8-62.0) and erlotinib group was 39.6% (95% CI, 25.7-53.4) (p=0.411). The median progression-free survival of gefitinib and erlotinib were 4.9 months (95% CI,
The Overexpression of Ribonucleotide Reductase Regulatory Subunit M1 (RRM1) Protein Is a Predictor of Shorter Survival to Gemcitabine-based Chemotherapy in Advanced Non-small Cell Lung Cancer (NSCLC)

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Background: RRM1, the regulatory subunit of ribonucleotide reductase, is associated with resistant to gemcitabine. There are few studies to analyze the prognosis according to RRM1 protein expression by immunohistochemical (IHC) stain. We evaluated whether RRM1 protein expression is predictor to survival and response in gemcitabine-treated, advanced NSCLC.

Methods: We retrospectively collected 40 formalin-fixed, paraffin-embedded tumor tissues of NSCLC to investigate the protein expression of RRM1 by IHC stain. Purified rabbit anti-human RRM1 polyclonal antibody (ProteinTech Group, Chicago, IL, USA) was used for IHC stain of RRM1. It was defined as RRM1-positive tumor to be grade 3 of intensity scale and more than half of proportion score out of the tumor tissue. Survival rate was analyzed with Kaplan-Meier method and the response with WHO criteria.

Results: Among 40 tumors, RRM1 expression was positive in 14 (35%) and negative in 26 (65%). All forty patients were treated with gemcitabine-based combination therapy as first-line for 10 (25%) patients or second-line for 30 (75%) patients. The therapeutic regimens were gemcitabine/platinum or gemcitabine/vinorelbine. As first-line therapy, gemcitabine/platinum was administered to 7 patients and gemcitabine/vinorelbine to 3 patients. All previous treated patients were refractory to paclitaxel/platinum and received gemcitabine/vinorelbine as second-line therapy. Median age was 61 years and M/F was 31/9. Stage IIIIB/IV was 7/33 and adenocarcinoma/squamous cell carcinoma/other cell type was 20/16/4. Any characteristics including age, gender, stage, cell type and first/second-line were not statistically different between RRM-positive and RRM-negative groups. Overall survival of RRM1-positive groups was significantly shorter than that of RRM-negative groups (20.3 weeks vs. 51.7 weeks, p=0.022). Progression-free survival of RRM1-positive groups was significantly shorter than that of RRM-negative groups (6.4 weeks vs. 10.4 weeks, p=0.022). The response rates of 38 patients out of all 40 patients were assessable. Among RRM1-positive groups, PR was 1 (7.7%) patients, SD 2 (15.4%) and PD 10 (76.9%). Among RRM1-negative groups, PR was 6 (24.0%) patients, SD 8 (32.0%) and PD 11 (44.0%). Disease control rate (PR+SD) of RRM1-positive groups was significantly lower than that of RRM-negative groups (23.1% vs. 56%, p=0.05) but the response rate was not different between two groups (p=0.149).

Conclusion: In patients with gemcitabine-based treated, advanced NSCLC, patients with RRM1-positive tumors were worse in overall survival, progression-free survival and disease control rate than patients with RRM1-negative tumors. These results strongly suggest that IHC overexpression of RRM1s is a significant predictor of survival and disease stabilization to gemcitabine-based chemotherapy in advanced NSCLC.

Keywords: NSCLC, RRM1, Immunohistochemistry

Second Line Chemotherapy with S-1 for Head and Neck Cancer

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Background: Combination chemotherapy with cisplatin and 5-FU is one of the effective regimens for head and neck cancer, S-1 is an oral anticancer agent, metabolically activated prodrug of 5-FU. We retrospectively evaluated the efficacy of S-1 therapy as second-line treatment for patients with head and neck cancer that was refractory to first line therapy or recurrent after treatment.

Methods: The patients eligible for our study had to have measurable, histologically confirmed squamous cell carcinoma of the head and neck; stage IV; refractory to previous treatment or recurrent disease; adequate organ function; age 20-80 years; and a performance status of two or less. Cisplatin was infused over one hour on day one (75 mg/m²) and S-1 was administered orally for 14 consecutive days (days two to 15). The dosages of S-1 were calculated according to the patients’ body surface (80 mg/m²/day). Each course was repeated every three weeks. After two
courses, tumour response was evaluated by computed tomography and laryngoscopy.

Results: From September 2005 to July 2009, S-1 was administered to 23 patients with refractory or recurrent head and neck cancer after first line therapy. Of these 23 patients, 10 patients were additionally administered cisplatin.

The median age of the patients was 61 years, and males were predominant (19 male patients and 4 female patients). The median follow up duration was 17 months. In 23 patients, 11 patients (48.6%) achieved PR and 5 patients (21.7%) achieved SD, and PD in 7 patients (30.4%), respectively. Three year estimated survival rate was 43.4%.

The 3-year progression free survival was 19.8%. The most frequent moderate-to-severe toxicity was neutropenia, and grade 3 neutropenia occurred in 5 case and there was no clinically significant infection. There were two episode of grade2 anemia. Grade2 fatigue was noted in one patient.

Conclusion: S-1 is considered to be active agent recurrent and/or metastatic head and neck cancer as second line salvage chemotherapy. S-1 therapy is a useful anticancer treatment while maintaining patients quality of life in advanced head and neck cancer. The efficacy and adverse effect of cisplatin plus S-1 should be studied in carefully designed phase II/III trials.

The Metabolic Tumor Volume Predicts for Response to Treatment and Progression Free Survival in Head and Neck Cancer

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Background: To evaluate the prognostic value of metabolic tumor volume measured on 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) imaging and other clinical factors in patients treated for locally advanced head-and-neck cancer (HNC) at a single institution.

Methods: Between June 2005 and August 2008, fifty nine patients with HNC who underwent pretreatment FDG-PET studies received neoadjuvant chemotherapy and radiation therapy. Metabolically active tumor regions were delineated on pretreatment PET scans by a fixed SUV of 2.5. We evaluated the relationship of 18F-fluorodeoxyglucose-PET maximum standardized uptake value (SUV) and metabolic tumor volume (MTV) with response to treatment, progression-free survival (PFS) and overall survival (OS).

Results: The average SUVmax was 8.9 (range, 1.4-78.0) and the mean MTV was 23.5 cm³ (range, 1.2-170.8) for all patients. Higher MTV was associated with an increased risk of lymph node metastasis at diagnosis (p=0.028) and response to treatment (p=0.026). A Cox proportional-hazards model for progression free survival from head and neck cancer was used to evaluate sex, age, organ, stage, T-stage, lymph node metastasis, MTV, and SUVmax and neoadjuvant chemotherapy type. The results indicated that MTV was the only significant independent factor (p=0.021). A higher MTV of 9.3 cm³ (median MTV) was significantly associated with an increased hazard of recurrence (2.19-fold, p=0.007). We did not find a significant relationship of maximum SUV, stage, or other clinical factors with response to treatment or PFS or OS.

Conclusion: Metabolic tumor volume is an adverse predictive factor for treatment response and disease progression in HNC. MTV is a direct measure of tumor burden and is a potentially valuable tool for risk stratification and guiding treatment in future studies.

A Phase II Study of Combination Chemotherapy with Capecitabine and Cisplatin in Patients with Metastatic or Recurrent Head and Neck Cancer

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Background: Capecitabine is an oral fluoropyrimidine carbamute that mimic continuous infusion of 5-FU without the complications and inconvenience associated indwelling venous access. And clinically proven activity of the cisplatin/5-FU combination chemotherapy in patients with advanced squamous cell carcinoma of head and neck (SCCHN) supports the rationale for a clinical evaluation of capecitabine/cisplatin (XP) combination in metastatic or recurrent SCCHN. The purpose of this study was to assess the efficacy and toxicity of XP combination chemotherapy in patients with metastatic or recurrent SCCHN.

Methods: The study design was a prospective, open-label, non-blind, non-randomized single center phase II study. Between May 2003 and December 2006, 36 patients with histologically confirmed metastatic or recurrent squamous cell carcinoma of head and neck were enrolled. One chemotherapy cycle consisted of capecitabine 1,250 mg/m² orally twice a day on day 1 to 14 and cisplatin 60 mg/m² intravenously on day 1. Each cycle was repeated every 3 weeks. Maximum cycles of treatment were 6 cycles.

Results: Of the 36 patients, 33 patients were evaluable for tumor response. 18 patients achieved partial response, and 5 patients had stable disease. The overall response rate was 50.0%. The median time to progression was 3.7 months (95% CI, 2.1-5.3 months), with the median response duration of 4.9 months (Range, 1.6-18.6 months). And the median overall survival (OS) and 1-year OS rate were 10.3 months (95% CI, 8.5-12.1 months) and 43.3%.
Immunohistochemical Study to Identify Biomolecular Markers for Prediction of Outcomes of Radiotherapy for Nasopharyngeal Carcinoma

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Background: NPC is sensitive to radiotherapy and it can be cured with radiotherapy (RT) or concurrent chemoradiotherapy (CCRT). However, the treatment outcomes are variable even in same staged patients. In addition to the clinical prognostic factors such as gender, age and stage, biomolecular characteristics of the tumor may affect the treatment outcome. If proper prognostic factors such as biomolecular markers are identified, we could provide a more tailored therapy for each patient and achieve better treatment outcomes. We performed immunohistochemical study with pre-treatment biopsy specimens to identify biomolecular markers for prediction of outcomes of radiotherapy for nasopharyngeal carcinoma (NPC).

Methods: From January 1998 through December 2006, 68 patients were histologically diagnosed as non-metastatic NPC and treated with RT at Seoul National University Hospital. Only 38 patients had the paraffin block for the immunohistochemical study. Thirty-two patients (84%) had advanced stage NPC (2002 AJCC Stage III-IV). All patients, except for 6, were treated with induction chemotherapy with two or three cycles of cisplatin based regimen followed by either RT alone or CCRT with cisplatin. Immunohistochemical staining was done for Met, COX-2, EGFR, nm23-H1, p63, Cathepsin-D, p53, C-erbB2, CD138, STAT5, Egr1, CSE1L, STAT3 and LIN28 with the usual methods.

Results: The median follow-up time was 30 months (range, 11-83 months). Thirty-five patients were MTX positive and 22 patients showed high expression (58%). Twenty-seven patients exhibited CD138 and 17 patients showed high grade (45%). Twenty-two patients showed Egr1 expression (58%). High Met and CD138 expression were statistically significant negative prognostic factors on survival. The expression of Egr1 had a positive prognostic effect on progression-free survival and overall survival. The combined score (CS) of these three prognostic factors, Met (0, low; 1, high) plus CD138 (0, negative; 1, positive), was a strong prognostic factor. The median survival curve was distinctly separated according to this combined score (median survival: CS -1 or 0, 76 mo; CS 1, 71 mo; CS 2, 42 mo; CS 3, 24 mo, p=0.001). No prognostic value was revealed in COX-2, EGFR, nm23-H1, p63, Cathepsin-D, p53, C-erbB2, STAT5, CSE1L, STAT3 and LIN28.

Conclusion: The combined score of Met, CD138 and Egr1 could be used to stratify biomolecular risk groups.

Keywords: Nasopharyngeal carcinoma, Biomolecular markers, Immunohistochemical staining

Intensity-modulated Radiotherapy for Carcinoma of Oropharynx and Oral Cavity: Treatment Outcome and Complication

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Background: To assess the treatment outcomes and complications in the patients with oropharyngeal and oral cavity cancer treated with intensity-modulated radiotherapy (IMRT).

Methods: Nineteen patients with oropharyngeal and oral cavity cancer treated with definitive radiotherapy using IMRT between January 2002 and December 2007 were retrospectively analyzed. Among these patients, 7 patients were treated with Tomotherapy. Fourteen patients received concurrent chemotherapy. The primary site was tonsil in 8, base of tongue in 8, floor of mouth in 2 and oral tongue in 1 patient. Seventeen patients were squamous cell carcinoma and 2 patients, undifferentiated carcinoma. The median follow-up for all patients was 29 months (range 2-52 months). Thirteen patients (68.4%) had stage IV disease, 3 patients (15.8%) had stage III and 3 patients (15.8%) had stage II disease. The median prescription dose to gross target volume was 70 (65.7-76.3) Gy, and the median daily fractional dose was 2.12 (2.12-2.35) Gy. For patients with cervical lymph node metastasis, the median involved neck dose was 59.4 (54-70) Gy. The median elective neck dose was 56.1 (51-60) Gy.

Results: Three locoregional failures and 1 distant metastasis were observed. Two patients died of disease and 2 patients died of intercurrent disease. Two year overall survival rate was 73.7%, 2-year disease-free survival rate was 78.9% and 2-year locoregional control rate was 84.2%. Late toxicities were as follows: 7 patients with grade 1 xerostomia and 2 patients with grade 2 xerostomia and 3 patients had intolerance for spicy foods.

Conclusion: IMRT is effective and feasible for the patients with oropharyngeal and oral cavity cancer including those
with advanced disease as a definitive treatment modality without serious complications.

**Keywords:** Intensity-modulated radiotherapy, Tomotherapy, Oropharyngeal cancer, Oral cavity cancer

**P-48**

Comparison of Clinical Features and Treatment Outcome in Elderly Head and Neck Cancer Patients with Younger Patients

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**Background:** The elderly patients often receive treatment less intensive than the younger patients because of age-related organ dysfunctions, comorbidities, and poor tolerance to treatment. However, recent data reported that elderly patients are tolerable to chemotherapy and radiotherapy as much as younger patients. So we analyzed clinical data of elderly head and cancer patients to compare clinical features and treatment outcome with younger patients.

**Methods:** We analyzed the clinical data of 180 head and neck cancer patients who were diagnosed at our center retrospectively, from January 2001 to December 2008. The analysis was conducted to compare clinical features and treatment outcome between elderly patients (EP ≥ 70 years old) and younger patients (YP < 70 years old). Patients with thyroid cancer, lymphoma, sarcoma, skin cancer were excluded for analysis.

**Results:** The number of elderly patients were 57 (57/180, 31.7%). No sex (male: E = 84.2% : 88.6%, p = 0.413), histology (squamous cell, E: Y = 94.7% : 88.6%, p = 0.615) and amount of smoking (> 40 PYS, E: Y = 82.5% : 78.9%) differences were observed. The difference of involving primary site was not also observed except nasopharynx (oral cavity, E: Y = 14% : 13.9%, p = 0.433, oropharynx, E: Y = 8.8% : 8.3%, p = 0.45, larynx E: Y = 33.3% : 36%, p = 0.54, sinus, E: Y = 14% : 11.1%, p = 0.67). Involvement of nasopharynx was less frequent in the elderly (E: Y = 8.8% : 15.6%, p = 0.02). The advanced stage was more common in the elderly (E: Y = 12.3% : 4.1%, p = 0.07). The younger patients showed good PS rather than elderly patients (PS 0-1, E: Y = 94.2% : 66.1%, p = 0.02). Concurrent chemoradiation were conducted more frequent in the younger (E: Y = 7.2% : 22.5%, p = 0.03) but not induction chemotherapy followed by radiotherapy (E: Y = 21.5% : 20.8%, p = 0.29). Best supportive care was performed more frequent in the elderly (E: Y = 12.5% : 1.7%, p = 0.04). The patients who complete radiotherapy were more frequent in younger patients (E: Y = 89.3% : 98.9%, p = 0.01) and total radiation dose were received were also more in the younger (E: Y = 59 Gy : 64.3 Gy, p = 0.01). The median overall survival of patients received curative treatment was longer in the young patients (E: Y = 16.6 months (3-120) : 24 months (1.0-180), p = 0.03).

**Conclusion:** The elderly and neck cancer patients have similar clinical characteristics but treatment pattern, tolerance to radiotherapy and outcome were different than younger patients.

**Keywords:** Head and neck cancer, Elderly and younger, Clinical features

**P-49**

Update of a Phase II Trial of Induction Chemotherapy with Docetaxel/Capecitabine (DC) for Patients with Locally Advanced Head and Neck Cancer

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**Background:** Capecitabine (C) is an oral fluoropyrimidine that is preferentially activated in tumor tissues. Thymidine phosphorylase (TP) is an enzyme that converts capecitabine to 5-FU in tumor cells. The combination of docetaxel and capecitabine has shown synergism in preclinical studies. In addition, docetaxel and 5-FU have shown activity in head and neck cancer. We updated survival data of a phase II trial of DC induction chemotherapy in locally advanced head and neck cancer.

**Methods:** Between June 2001 and December 2003, 34 patients were enrolled. The treatment schedule consisted of D 75 mg/m² IV on day 1 and C 850 mg/m² PO BID on days 1-14, every 3 weeks. After 3 cycles of chemotherapy, all patients received radiotherapy up to 75 Gy of doses.

**Results:** Median age was 65 years old (33-77). The subjects included 31 males and 3 females with disease in the nasopharynx (7), oral cavity (4), oropharynx (4), hypopharynx (4), and larynx (15). The staging was III/IV=12/22, with 28 squamous cell and 6 undifferentiated cell and PS 0/1/2=2/25/6. Eight patients did not complete treatment. The dose intensity was 98.2% (D 97.9%, C 98.4%). Grade 3/4 hematologic toxicities included 5 neutropenia (4.8%) and 2 neutropenic fever (1.9%). Grade 2/3 non-hematologic toxicities included 13 myalgia (12.6%), 25 oral mucositis (24.4%), 3 hand-foot syndrome (2.9%), 4 diarrhea (3.9%),...
Phase II Study of Docetaxel, Cisplatin and 5-FU Induction Chemotherapy Followed by Chemoradiotherapy in Advanced Nasopharyngeal Cancer

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Background: This study sought to determine the feasibility and safety of induction chemotherapy with docetaxel, cisplatin, and 5-fluorouracil (5-FU) in combination (TPF) followed by concurrent chemoradiotherapy (CCRT) for advanced nasopharyngeal cancer (NPC).

Methods: Patients with advanced NPC were treated with three cycles of induction chemotherapy. Docetaxel (70 mg/m²) and cisplatin (75 mg/m²) were given on day 1, followed by 5-FU (1,000 mg/m²) as a continuous infusion for 4 days. After induction chemotherapy, cisplatin was given at a dose of 100 mg/m² every 3 weeks with radiotherapy.

Results: Thirty-three patients were enrolled; all patients were stage III (n=4, 12.1%) or IV (n=29, 87.9%). Among the patients, 32 patients completed both induction TPF therapy and CCRT, with responses as follows: five patients (15.2%) achieved a complete response (CR), and 27 patients (81.8%) a partial response (PR). At 6 weeks after CCRT, 23 patients (69.7%) had a CR and nine patients (27.3%) a PR. The 3-year progression-free survival was 75.6% and the 3-year overall survival was 86.1%. Neutropenia (72.7%), febrile neutropenia (9.1%), and nausea (9.1%) were the most severe toxicities (grade 3-4) during induction chemotherapy, and mucositis (39.4%), fatigue (15.2%), and nausea (9.1%) were the most common toxicities (grade 3-4) during CCRT.

Conclusion: Although most patients had stage IV NPC, the TPF induction chemotherapy followed by CCRT showed promising activity with manageable toxicity. These results demonstrated the possibility of effective treatment with the aim of not only a palliative, but also a curative, approach to the treatment of advanced NPC.

Keywords: Nasopharyngeal carcinoma, Docetaxel, Induction chemotherapy, Chemoradiotherapy

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A Phase II Study of Gemcitabine, 5-FU and Cisplatin Combination Chemotherapy for Patients with Advanced Biliary Tract Cancer

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Background: Biliary tract cancer is an uncommon malignancy with grave prognosis. For the metastatic or recurrent biliary tract cancer, there are only few treatment options without known standard chemotherapy regimen. However, recent trials elucidated the activities of gemcitabine for this tumor. 5-FU and cisplatin were used traditionally and these drugs have modest efficacies for biliary tract cancer. With expectation of synergism, we explored the above triple drug combination regimen for the patients with biliary tract cancer.

Methods: Eligibility criteria is as follows; histologically confirmed adenocarcinoma of biliary tract, gall bladder or ampulla of Vater; unresectable or metastatic cancer, 2-dimensionally measurable lesions, good performance status with ECOG 0-2, age 18-70, normal bone marrow, renal and hepatic functions, informed written consent and chemotherapy-naive. Treatment regimen is as follows; gemcitabine 800 mg/m² was administered on day 1 and 8, 5-FU 1 g/m²/day 24 hours continuous infusion from day 1 to day 4 and cisplatin 60 mg/m² on day 2. This regimen was repeated every 3 weeks.

Results: From Sep 2003 to Oct 2008, a total of 31 patients (17 gall bladder adenocarcinoma, 7 extrahepatic cholangiocarcinoma and 7 intrahepatic cholangiocarcinoma) were entered into this study. Median age was 56 years (range 34-67). 30 patients were evaluable for their responses. One patient expired with an unknown cause after 2 cycles of treatment before re-evaluation. Partial responses were obtained in 8 patients (response rate 26.7%, 95% CI 10.5-42.9%). The median time to progression and overall survival duration were 6.4 months and 9.8 months, respectively. Among total 172 cycles, grade 3 or 4 granulocytopenia and thrombocytopenia were observed in 18.0% and 29.1%, respectively. Among total 31 patients, grade 3 or 4 nausea and vomiting were observed in 32.3% and 16.1%, respectively. Six patients experienced neutropenic fever episodes.

Conclusion: Gemcitabine, 5-FU and cisplatin combination chemotherapy was active for the patients with advanced biliary tract cancer. The toxicities of this triple drug regimen were tolerable to most patients.

Keywords: Gemcitabine, 5-fluorouracil, Cisplatin, Biliary
Stereotactic Body Radiotherapy for the Patients with Primary Unresectable Hepatocellular Carcinoma: Dosimetric Parameters Predicting the Hepatic Complication

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Background: To evaluate the hepatic complication in the patients with small-sized hepatocellular carcinoma (HCC), who were treated with hypofractionated stereotactic body radiotherapy (SBRT) and to identify the predicting parameters to cause the hepatic toxicity and the deterioration of hepatic function.

Methods: From April 2004 to May 2007, 47 patients with small unresectable primary HCC received SBRT using Cyberknife at the Cyberknife center, the Catholic University of Korea. Of those, 36 patients did not receive any other local treatment influencing the hepatic function at least 3 months after the completion of SBRT. To assess the deterioration of hepatic function, we evaluated the presence or absence of the progression of CP class. The gross tumor volume (GTV) were 18.3±15.9 cm³ (range: 3.0-81.3 cm³) and the total dose administered were 30-39 Gy (median: 36 Gy). To identify the parameters for predicting the radiation-induced hepatic toxicity and the deterioration of the hepatic function, the clinical parameters (gender, age, ECOG performance status, AJCC stage, previous surgery and liver transplantation) and the dosimetric parameters (total liver volume, normal liver volume, GTV, the total liver volume receiving <18 Gy (rV18Gy)) were evaluated.

Results: Of 36 patients, 12 patients (33%) developed Grade 2 or higher hepatic toxicity and 4 patients (11%) developed the progression of CP class. Most patients had recovered from Grade 2 or higher hepatic toxicity after median 2 months but only one patient persisted without recovery, who was one of the patients with the progression of CP class. On multivariate analysis, the only significant parameter associated with the progression of CP class was the total liver volume receiving <18 Gy (rV18Gy) (p=0.05, CI: 0.973-0.999).

Conclusion: The progression of CP class after SBRT limits additional other local treatment and reflects the deterioration of hepatic function. Therefore, it would be appropriate to consider that the presence or absence of the progression of CP class is a dose-limiting toxicity. The total liver volume receiving <18 Gy (rV18Gy) was a significant parameter predicting the risk of the progression of CP class and it should be >800 cm³ to reduce the risk of the deterioration of hepatic function.

Keywords: Hepatocellular carcinoma (HCC), Stereotactic body radiotherapy (SBRT), Radiation-induced hepatic toxicity (RIHT), Child-Pugh class (CP class)

Sorafenib for Recurrent Hepatocellular Carcinoma after Liver Transplantation


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Background: Sorafenib is the only drug that has shown a survival benefit in patients with hepatocellular carcinoma (HCC) in randomized phase 3 trials. The efficacy and safety of sorafenib in the treatment of recurrent HCC after liver transplantation, however, has not been determined.

Methods: We retrospectively analyzed 13 patients who were treated with sorafenib for recurrent HCC after liver transplantation.

Results: All 13 patients underwent living-donor liver transplantation for HCC with underlying liver cirrhosis caused by hepatitis B virus (HBV) infection. The median Model for End-Stage Liver Disease (MELD) score at transplantation was 7.6 (range, 4.2-25.2). The median time from liver transplantation to detection of recurrent HCC was 12.3 months (range, 0.5-33.4 months). The median serum alpha-fetoprotein (AFP) concentration before sorafenib administration was 193 ng/mL (range, 1-20,500 ng/mL). Eleven of 13 patients had a starting dose of 400mg twice daily and two had a starting dose of 200 mg twice daily at the discretion of the attending physician. The median duration of sorafenib treatment was 2.4 months (range, 0.3-9.9 months). Single or multiple immunosuppressants were co-administered in these patients during sorafenib treatment. Six of 10 evaluable patients showed stable disease, which was the best response and the median duration of stabilization was 3.9 months (95% confidence interval [CI], 1.6-6.2 months). At a median follow-up duration of 3.7 months (range, 0.3-10.9 months) in living patients, the median progression-free survival and the median overall survival from commencement of sorafenib were 2.9 months (95% CI, 1.2-4.6 months) and 5.4 months (95% CI, 3.7-7.0 months), respectively. Grade 3 neutropenia was observed in one patient, which was the only high grade hematologic toxicity.
observed. Grade 3 hand-foot skin reactions were observed in three patients. Adverse events could be managed with dose adjustment.

**Conclusion:** These findings suggest that the efficacy of sorafenib for recurrent HCC after liver transplantation may not be inferior to that observed in phase 3 trials conducted in non-transplant patients and the drug may be safely administered with careful monitoring in these patients.

**Keywords:** Sorafenib, Hepatocellular carcinoma, Liver transplantation, Immunosuppressant

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**The Significance of ICG R15 in Predicting Radiation-induced Hepatic Toxicity for Radiotherapy of Hepatocellular Carcinoma Patients**

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**Background:** The purpose of this study was to investigate the significance of indocyanine green retention rate at 15 minutes (ICG R15) in predicting radiation-induced hepatic toxicity in hepatocellular carcinoma (HCC) patients treated with radiotherapy (RT).

**Methods:** A total of 309 patients who underwent RT for HCC from January 1992 to December 2007 were reviewed. Level of liver cirrhosis was Child-Pugh (CP) class A in 263 patients (85.1%) and CP class B in 46 patients (14.9%). The median RT dose was 45 Gy (range 30-65) in 1.8-3 Gy daily fraction. Patients were evaluated for any hepatic toxicity by biochemical parameters including albumin, total bilirubin (T.Bil), AST, ALT, ALP, platelet, prothrombin time (PT INR) before and 1, 4, and 6 months after RT. ICG R15 was measured prior to and within 1 month after completion of RT. Radiation induced liver disease (RILD) was defined as Grade 3 or 4 hepatic toxicity according to the Common Toxicity Criteria of the National Cancer Institute. All patients were evaluated for RILD within 4 months after RT.

**Results:** All patients underwent ICG R15 test before RT. Paired ICG R15 test before and after RT was done in 84 patients. Pretreatment ICG R15 ranged from 1 to 79% with median of 11%. A total of 22 patients (7.1%) developed RILD. The pretreatment ICG R15 level showed no significant correlation with RILD. However, the patients with pretreatment ICG R15 ≥30% presented significantly high incidence of grade 3 or 4 acute thrombocytopenia (9.1% vs 23.8%, \( p=0.005 \)) and grade 3 or 4 acute hyperbilirubinemia (5.9% vs 27.9%, \( p=0.000 \)). This patients also presented severe chronic hyperbilirubinemia (16% vs 39.5%, \( p=0.001 \)) and severe chronic thrombocytopenia (8.4% vs 28.9%, \( p=0.000 \)). The change in pre-and post-RT ICG R15 showed significant correlation with toxicity; in patients showing 15% increase of post-RT ICG R15, RILD significantly increased (5.3% vs 22.2%, \( p=0.019 \)) as well as grade 3 or 4 acute AST elevation (1.9% vs 19.2%, \( p=0.006 \)).

**Conclusion:** The pretreatment ICG R15 ≥30% was the significant factor affecting hepatic toxicity. The ICG R15 increment of ≥15% after completing radiotherapy was significantly associated with RILD. ICG R15 can be used to predict hepatic toxicity including RILD.

**Keywords:** Hepatocellular carcinoma, Radiotherapy, Indocyanine green, Radiation-induced hepatic toxicity

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**Clinical and Prognostic Features of Solitary Plasmacytoma: Outcome Analysis of 29 Cases in SNUH**

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**Background:** Solitary plasmacytomas are rare tumors and account for less than 10% of plasma cell neoplasms. There are two main categories of clinical presentation: bone involvement (solitary plasmacytoma of bone: SBP) or soft tissue disease (extramedullary plasmacytoma: EMP). Long-term disease free survival and cure is possible. But, progression to MM remains the main problem. The objective of this study is to examine the clinical features and to identify the outcomes of prognostic factors of solitary plasmacytoma.

**Methods:** The data from 29 patients with solitary plasmacytoma (SP) diagnosed in Seoul National University Hospital from 1986 to 2008 were collected. The median age was 60 years old with the range of 30 through 76, and the ratio of male to female was 1.9 : 1. Among 29 patients, 22 were solitary plasmacytoma of bone (SBP), and 7 were extramedullary plasmacytoma (EMP). The therapies that the patients received were: radiotherapy (RT) alone (n=15), surgery and radiotherapy (n=9), surgery alone (n=4), and chemotherapy alone (n=1). The median radiation dose was 4460 cGy (range 2340-5600). The median follow-up was 3.32 years (range 0.78-14.11).

**Results:** The 5-year overall survival (OS) rate was 60%; the 5-year progression free survival (PFS) rate was 42%; the 5-year relapse free survival (RFS) was 88%; and the 5-year multiple myeloma free survival (MMFS) was 72%. The common sites of SBP included vertebral bodies (n=12), and pelvic bone (n=4). Most EMPs occurred in the oronasopharynx (n=4). The pattern of failure in 22 patients with SBP manifested as distant relapse in three (median times: 18.5 month), and progression to multiple myeloma (MM) in five (median time: 19 month). There were two progressions to other diseases in SBP group. One patient was diagnosed renal amyloidosis at 47 months and the other...
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Results: Cycles of alternating CODOX-M/IVAC. (n=30) patients received 3 cycles of CODOX-M and 4 cycles of CODOX-M/IVAC between January 1996 and September 2008 were analyzed for overall response rate (ORR), OS, event-free survival (EFS), and toxicity. Low-risk (n=3) and high-risk (n=27) were not statistically significant. In terms of ORR alone, surgery and RT, surgery alone, and chemotherapy alone were not statistically significant. In terms of RT dose, there was no dose-response relationship for all outcomes.

Conclusion: Solitary plasmacytoma presents excellent local control rates. However, progression to MM remains the main problem. The development of other diseases related to plasmacytoma occurred later than other failures. Therefore, we suggest that long term follow-up, considering other disease, is necessary.

Keywords: Solitary plasmacytoma, Prognostic factor, Amyloidosis, POEMS

Efficacy of CODOX-M/IVAC in Patients with Adult Burkitt’s Lymphoma (BL)

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Background: CODOX-M/IVAC regimen (cyclophosphamide, vincristine, doxorubicin, and methotrexate/ifosfamide, etoposide and cytarabine) is originally developed for pediatric BL. When used in adult BL, it resulted in 2-year overall survival (OS) of 72.8%. This study was undertaken to evaluate the efficacy and toxicity of CODOX-M/IVAC in adult BL.

Methods: Thirty-three BL patients treated with CODOX-M/IVAC between January 1996 and September 2008 were analyzed for overall response rate (ORR), OS, event-free survival (EFS) and toxicity. Low-risk (n=3) and high-risk (n=30) patients received 3 cycles of CODOX-M and 4 cycles of alternating CODOX-M/IVAC.

Results: After a median follow-up of 37.4 months (12.7-75.6 months), 2-year OSes were 100% and 49% and 2-year EFS were 100% and 42% for low-risk and high-risk groups, respectively. ORRs were 100% for low-risk group and 56.6% for high-risk group. Median OS and EFS in high risk group were 9.1 and 7.2 months. EFS and OS were significantly inferior in patients who received delayed schedule of CODOX-M/IVAC (p=0.026 and p=0.010) and those who failed to complete CODOX-M/IVAC (p=0.001 and p=0.003). Nineteen patients (63.3%) of high-risk patients completed planned schedule. Eleven (36.7%) of high-risk patients were not able to complete planned schedule due to the toxicities. Grade 3 or 4 neutropenia was observed in 92.9-100% in each cycle. Grade 3 or 4 non-hematologic adverse events included CNS toxicity (3 cases), renal toxicity requiring renal replacement therapy (4 cases), hepatic toxicity (3 cases) and severe mucositis (3 cases). Two treatment-related deaths were attributable to uncontrolled infection.

Conclusion: CODOX-M/IVAC is an effective regimen for adult BL patients. However, considering high rates of toxicity and incomplete schedule, dose-modified CODOX-M/IVAC is necessary for Korean patients with adult BL.

Keywords: Burkitt’s lymphoma, CODOX-M/IVAC

Efficacy of L-asparaginase-based Chemotherapy in Patients with Extranodal NK/T Cell Lymphoma

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Background: This study was planned to evaluate the efficacy of L-asparaginase-based chemotherapy for chemotherapy-naive and refractory/refractory patients with extranodal NK/T cell lymphoma (NTCL).

Methods: Twenty-six patients diagnosed with NTCL between September 2002 and July 2009 at Seoul National University Hospital received L-asparaginase-based chemotherapy as a first-line (n=16) or palliative (n=10) setting. Overall response rate, progression-free survival (PFS), and overall survival (OS) were calculated.

Results: Sixteen chemotherapy-naive NTCL patients (upper aero/digestive tract [UAT], 10 patients; and non-UAT, 6) received IMEP (ifosfamide, methotrexate, etoposide, and steroid)-like regimen. These patients had high frequencies of stage II/IV (11 patients, 68.7%), high lactate dehydrogenase level (13, 81.3%), and B symptoms (13, 81.3%). After four median cycles of chemotherapy (range, 1-8 cycles) and 15 median doses of L-asparaginase (range, 1-80 doses), 12 (85%) of 14 evaluable patients showed objective response. Median PFS and OS were 6.5 months and 20.5 months, respectively. Ten relapsed or refractory patients had UAT-NTCL (n=6) and non-UAT NTCL (n=4). After the median 11 doses of L-asparaginase (range, 4-34 doses), objective response rate was 71% (5 of 7 evaluable patients) and median PFS and OS were 8.3 months and 4.2 months, respectively. The major adverse events included myelosuppression (grade 4 neutropenia, 73%; and neutropenic fever, 15%), elevation of liver transaminase, hypoalbuminemia, and hypofibrinogenemia. Thirteen patients (50%) received cryoprecipitate because of hypofibrinogenemia and gastrointestinal bleeding happened in one patient with intestinal involvement of lymphoma. Three patients developed hypersensitivity reaction and one of them had anaphylactic shock and stopped treatment.

Conclusion: L-asparaginase-based chemotherapy is promising in extranodal NK/T cell lymphoma as a first line and
A Case of Monoclonal Gammopathy in Extranodal Marginal Zone B-cell Lymphoma (ENMZL)

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Monoclonal gammopathy is a well-known occurrence in splenic marginal zone lymphoma (MZL). However, its prevalence has rarely been reported in ENMZL. A few cases show a strong correlation between the presence of a monoclonal spike and the involvement of bone marrow indicating more advanced disease. We experienced a 66-year-old man who was diagnosed with IgM monoclonal gammopathy in ENMZL. The patient was presented as iron deficiency anemia. During the work up under the suspicion of gastrointestinal bleeding, he had severe abdominal pain and it was revealed due to small bowel mass perforation. The mass was pathologically diagnosed as a ENMZL of mucosa-associated lymphoid tissue (MALT lymphoma) with focal large cell transformation (diffuse large B-cell lymphoma). The patient had stage IV disease with involvement of bone marrow and multiple abdominopelvic lymph nodes. Here we report a case of monoclonal gammopathy in ENMZL, because there is a no study about that in Korea till now.

Is Inactivation of O6-methylguanine DNA Methyltransferase Still a Favorable Prognostic Factor of Patients with Diffuse Large B-cell Lymphoma in the Era of R CHOP Chemotherapy?

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Background: The prognostic significance of O6-methylguanine DNA methyltransferase (MGMT) inactivation was evaluated in patients with diffuse large B-cell lymphoma (DLBCL) who received clophosphamide, doxorubicin, vincristine, and prednisone (CHOP) in addition to rituximab. Methods: In this retrospective study, we used the methyl-specific polymerase chain reaction to investigate MGMT promoter methylation status and immunohistochemistry to evaluate MGMT expression in DLBCL patients who received rituximab plus CHOP (R CHOP) chemotherapy.

Results: No difference in patient characteristics, disease characteristics, response, or survival in patients with DLBCL who received frontline R-CHOP chemotherapy was observed according to MGMT methylation status and MGMT expression. On multivariate analysis, grade 3/4 mucositis in the MGMT methylated group was significantly higher than that in the MGMT unmethylated group (HR 2.40, 95% CIs: 1.26-7.26, p=0.014).

Conclusion: This study demonstrated that inactivation of MGMT does not appear to play an important role in patients with DLBCL who received R-CHOP chemotherapy either with regard to the response rate or overall survival. Additionally, grade 3/4 mucositis was found to be significantly related with inactivation of MGMT by a multivariate analysis.

Keywords: Diffuse large B-cell lymphoma, O6-methylguanine DNA methyltransferase, Hypermethylation, Rituximab-CHOP

Salvage Therapy with Gemcitabine, Ifosfamide, Dexamethasone, and Oxaliplatin (GIDOX) for B-Cell Non-Hodgkin’s Lymphoma

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Background: We investigated response rates to and toxicities of gemcitabine, ifosfamide, dexamethasone, and oxaliplatin (GIDOX) for the treatment of relapsed or refractory aggressive B-cell non-Hodgkin lymphoma (NHL).

Methods: Patients with recurrent or refractory diffuse large B-cell lymphoma or mantle cell lymphoma (DLBCL) were eligible for enrollment in this study. Treatment consisted of gemcitabine 1,000 mg/m² intravenously (i.v.) on Days 1 and 8, ifosfamide 2000 mg/m² i.v. on Day 1, dexamethasone 40 mg orally on Days 1-4, and oxaliplatin 130 mg/m² i.v. on Day 2, every 21 days. The primary goal of treatment was to establish a response rate after three cycles. Afterwards, patients could proceed to high-dose treatment.
chemotherapy followed by autologous stem cell transplantation (HDC-ASCT) or receive up to six treatment cycles.

**Results:** Twenty-seven eligible patients were evaluated for toxicity and response. The median age of the patients was 54 years (range, 18-75 years), and most had DLBCL. After three cycles, there were four CR (15%) and 10 PR (37%) for an overall response rate (RR) of 52%. Among a total of 88 GIDOX cycles, grade 3 and 4 neutropenia occurred in 33% and 16% of the cycles, respectively. Likewise, grade 3 and 4 thrombocytopenia occurred in 14% and 16% of the cycles, respectively. Two patients (2%) experienced febrile neutropenia, while seven patients (26%) proceeded to HDC-ASCT.

**Conclusion:** GIDOX is an active salvage regimen for aggressive B-cell NHL and can be tolerated by patients with acceptable toxicity.

**Keywords:** Gemcitabine, Salvage therapy, Non-Hodgkin’s lymphoma

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**P-61**

**Concurrent Chemoradiotherapy with Weekly Docetaxel and Cisplatin in Advanced Esophageal Cancer**

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**Background:** How best to manage advanced esophageal cancer remains unresolved, especially in palliative care. To improve the symptoms, such as dysphagia, concurrent chemoradiotherapy has been used as treatment option for patients with advanced esophageal cancer. Recently, docetaxel has been widely used in esophageal cancer. Therefore this study was performed to determine the feasibility and safety of concurrent chemoradiotherapy with weekly docetaxel and cisplatin in advanced esophageal cancer.

**Methods:** Patient with locally advanced or metastatic esophageal squamous cell carcinoma who have adequate organ function were eligible. During chemoradiotherapy, docetaxel and cisplatin were given at a dose of 20 mg/m² and 25 mg/m², respectively at D1, D8, D15. This treatment schedule was repeated every 4 weeks. Two cycles of chemotherapy were delivered during radiotherapy. Radiotherapy was started at a dose of 180-200 cGy/day, up to a total dose of 4600-5400 cGy.

**Results:** All patients completed to concurrent chemoradiotherapy. In all, 24 patients could be assessed for treatment response. Twenty-five men and one woman were enrolled, with a median age of 61 years (range 50-71 years). ECOG performance status was 0/1/2=11/11/4; stage IIB/III/IVA/IVB=2/15/2/7. Complete response was achieved in 5 patients (19.2%), partial response in 13 (50%), stable disease in 5 (19.2%) and one patient had progressive disease (3.8%). Therefore the overall response rate was 69.2% and the disease control rate was 92.4%. Twenty-two patients had baseline dysphagia symptoms. Of these, dysphagia improved by more than one grade in 18 (86%). No greater than grade 3 hematologic toxicity including leucopenia, neutropenia, anemia, thrombocytopenia occurred during this study. The common non-hematologic toxicities were esophagitis, anemia and dermatitis. Greater than grade 3 esophagitis and dermatitis occurred in 5 patients (9.6%) and 2 patients (3.8%), respectively. Concurrent radiotherapy was interrupted in 4 patients, 2 patients due to grade 3 anemia, 2 patients due to personal reason. The dose of cisplatin was reduced in 1 patients due to nephrotoxicity. The D15 chemotherapy of second cycle was omitted only in 1 patients due to anemia and esophagitis. Of the scheduled docetaxel and cisplatin doses, 99.4% and 98.5% were administered, respectively.

**Conclusion:** The concurrent chemoradiotherapy with weekly docetaxel and cisplatin is found to be well-tolerated and seemed to be effective in advanced esophageal cancer with results of good efficacy in tumor control, but also improvement of symptoms. This treatment would be helpful palliative treatment or neoadjuvant treatment. However, a large-scale phase II or phase III clinical trial is needed to evaluate the role of weekly docetaxel and cisplatin compared to 5-FU and cisplatin in the concurrent chemoradiotherapy for esophageal cancer.

**Keywords:** Esophageal neoplasm, Chemoradiotherapy, Docetaxel, Cisplatin

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**P-62**

**The Safety and Effectiveness of Central Venous Catheterization in Patients with Cancer: A Prospective Observational Study**

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**Background:** Central venous catheterization (CVC) is frequently used to deliver chemotherapeutic drugs, blood products, parenteral nutrition, and other intravenous therapy in patients with cancer. This study investigated the safety and effectiveness of CVC in patients with cancer.

**Methods:** We prospectively enrolled the cancer patients who underwent CVC involving a subclavian venous catheter (PICC), chemo-port (CP), or Hickman catheter (HC) for various therapies in our department. No patient was given prophylactic antibiotics or anti-coagulation for infection or thrombosis. We assessed the complication rates associated with CVC and analyzed the catheter lifespan.

**Results:** From March 2007 to March 2009, 121 patients
underwent 189 episodes of CVC, including 63 males and 76 with solid malignancies. An SVC was inserted most frequently (86 cases, 43.9%), followed by CP (72 cases, 38.1%), HC (10 cases, 5.3%), and PICC (24 cases, 12.7%). There were 57 complications (31.25%): infection in 25 cases (13.2%), malposition or migration in 18 cases (9.5%), thrombosis in eight cases (4.2%), and bleeding in four cases (3.2%). Malposition or migration was observed more frequently with a PICC (p=0.000) than a SVC or CP; infection more often with a tunneled catheter than a non-tunneled catheter (p=0.008); and thrombosis in males more often than in females (p=0.041). The median catheter lifespan was 46 days (95% CI 33.6-58.4) and catheters were maintained successfully in 82 cases (63.1%) until the intended time (therapy completion, discharge, or death). The catheter lifespan was longer in solid cancer (median days, 64 vs. 35, p=0.007) than in hematologic cancer, with a CP (240 vs. 37 vs. 21, p=0.000) than a PICC or SVC, and for an indwelling catheter with image guidance (49 vs. 14, p=0.009) than a blind procedure, based on univariate and multivariate analyses.

**Conclusion:** Major problems related to CVC were infection, thrombosis, and malposition or migration. Unexpectedly, a PICC could not be maintained over a long time, due mainly to malposition or migration. CP was an effective tool for long-term use in patients with cancer.

**Keywords:** Central venous catheterization, Complication, Cancer

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**P-63**

Hypofractionated Intensity-Modulated Radiotherapy using Simultaneous Integrated Boost Technique with Concurrent and Adjuvant Temozolomide for Glioblastoma

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**Background:** We evaluated the clinical outcomes of combined hypofractionated intensity-modulated radiotherapy (IMRT) using simultaneous integrated boost technique (SIB) with temozolomide for patients with primary glioblastoma.

**Methods:** Thirty-nine patients with histologically confirmed primary glioblastoma were accrued between August 2004 and October 2007. Using a SIB technique, a dose of 50 Gy in 5-Gy fraction was prescribed to the gross tumor or surgical bed (GTV), 40 Gy in 4-Gy fraction and 30 Gy in 3-Gy fraction was delivered to 1- and 2-cm margin from the GTV, respectively. Concurrent temozolomide at a dose of 75 mg/m² per day during IMRT, followed by six cycles of adjuvant temozolomide at a dose of 150-200 mg/m² for 5 days were administered. Clinical results were defined by serial MR imaging and symptom deterioration. Treatment-related toxicities were graded according to the Radiation Therapy Oncology Group (RTOG) criteria.

**Results:** The median follow-up was 16.8 months (range 4.3-54.3 months). Tumor progression was observed in 28 patients (73.7%) and the median time to progression was 6.8 months. The median survival was 16.8 months and this was affected significantly by the extent of surgery (total resection vs. partial resection vs. biopsy: 26.3 months vs. 15.4 months vs. 11.6 months, p=0.001). Grade 3-4 hematologic or hepatic toxicity were observed in 5 patients (16.1%) during adjuvant temozolomide administration. Radiation necrosis was developed in 7 patients (18.4%) and massive necrosis, requiring second surgery, was observed in 3 patients (7.9%).

**Conclusion:** This regimen of hypofractionated IMRT with temozolomide showed an improved overall survival compared with that after conventional fractionation schedules. The treatment duration was also reduced from 6 weeks to 2 weeks. However, the incidence of brain necrosis was slightly increased with this treatment. Further study will be required to define the optimal fraction size for glioblastoma using highly conformal radiotherapy.

**Keywords:** Glioblastoma, Intensity-Modulated radiotherapy, Temozolomide

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**P-64**

2006 Cancer Pain Survey in Daegu-Gyeongbuk Area

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**Background:** The objectives of this cross-sectional survey study were to evaluate the prevalence and effect of pain in patients with cancer, to determine the methods of pain control being used by oncologists, to determine the degree of satisfaction perceived by the patients with cancer in response to physician’s pain management, and to assess the adequacy of the opioid prescription to control cancer pain.

**Methods:** The main sample consisted of 902 patients with cancer. These patients were seen at five university cancer centers and one community-based teaching hospital from October 2006 for 1 week. They came from inpatient and outpatient services of medical oncology departments and outpatient clinics of radiologic oncology. The sample consisted of all patients seen during the period of the study.
Our case suggested that MGCTs associated hematologic malignancies have grave prognosis like previous reports. Therefore, it is urgency to find optional treatment modality in these patients.

Keywords: Mediastinal germ cell tumor, MDS

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**Primary Mediastinal Germ Cell Tumors with Hematologic Disorders: A Case Report and Review of the Literature**

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Since Garnick et al. reported an association between hematological malignancies and mediastinal germ cell tumors (MGCTs) in 1983, several cases have been published. All MGCTs patients with hematologic malignancies had non-seminomatous type and died within 2 years after diagnosis of hematologic maligncies (median survival of 5 months). Isochromosome i(12p) was observed in 38% of these patients.

A 24-years-old man presented with chest pain and thrombocytopenia on March 2009. Percutaneous needle biopsy of anterior mediastinal mass showed yolk sac tumor and bone marrow examination revealed refractory cytopenia with unilineage dysplasia harboring i(12p). Positron emission tomography showed hypermetabolic lesions in anterior mediastinum, T spines, L3, and left pelvic bone. His disease was staged as TxN3M1bS2 (IIIC) and considered poor-risk by IGCCCG. He received three cycles of bleomycin, etoposide and cisplatin (BEP). Although BEP chemotherapy resulted in partial remission, it was interrupted due to severe thrombocytopenia and bleomycin hypersensitivity. Despite subsequent combination chemotherapy of paclitaxel, ifosfamide and cisplatin, his disease deteriorated rapidly and he died on August, 2009.

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**Concurrent Chemoradiotherapy Compared with Radiotherapy Alone in Intermediate-Risk Stage IB-IIA Cervical Cancer after Hysterectomy and Pelvic Lymphadenectomy**

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**Background:** To evaluate the benefit and toxicity of POCCRT in patients with intermediate-risk factors after radical hysterectomy and pelvic lymphadenectomy in FIGO stage IB-IIA cervical cancer as compared with PORT.

**Methods:** Between January 1990 and December 2007, 100 cervical cancer patients without high risk factors (lymph node metastasis, involved resection margin, and/or parametrial invasion) but with 2 or more of intermediate risk factors (deep stromal invasion, lympho-vascular space invasion, and large tumor diameter (> 4 cm)) underwent adjuvant radiation therapy with (n=50) or without concurrent chemotherapy (n=50). All patients received external beam radiotherapy with 50.0-50.4 Gy (median 50.4 Gy) to whole pelvis. The median follow-up time of POCCRT and PORT group were 5.4 and 9.4 years, respectively.

**Results:** Five-year overall survival (OS) and progression-free survival (PFS) of POCCRT vs. PORT group were 100% vs. 87% (p=0.012) and 94% vs. 83% (p=0.039), respectively. Pelvic failure-free survival rate (PFFR) was also better in POCCRT group (p=0.046). Distant metastasis-free survival rate was not different significantly (p=0.199). Acute grades 3 and 4 hematologic toxicity was more frequent in the POCCRT group (p<0.001). However acute grades 3 and 4 gastrointestinal (GI) and chronic toxicity were not different between two groups.

**Conclusion:** The addition of concurrent chemotherapy to PORT showed improved OS, PFS, PFFR without increasing acute GI and chronic toxicities in patients with intermediate-risk factors after radical surgery for stage IB-IIA cervical cancer.

**Keywords:** Cervical cancer, Postoperative radiotherapy, Chemotherapy, Intermediate risk factors
**Experience on Chemotherapy Related Neutropenic Fever Seen at Emergency Room of Inha University Hospital**

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**Background:** Neutropenic fever (NF) is potentially a life threatening complication of anti-cancer chemotherapy requiring prompt medical measures. Despite the urgency, the diagnosis and treatment may vary among institutions often dependent on competence of house officers at Emergency Room (ER). There has been limited data regarding the clinical outcome of patients with febrile neutropenia who were brought to ER.

**Methods:** Clinical findings, therapeutic outcomes, and risk factors of NF were evaluated on the retrospective analysis of 102 adult patients who visited ER from January 2006 through March 2009. NF was defined as a body temperature >38°C and absolute neutrophil count (ANC) >0.5×10⁹/L on the day of fever or the day after.

**Results:** The ECOG performance status (PS) was 0 in 15 patients, 1 in 67, and 2 in 20. The patients had a mean age of 57 years (range, 25-84). Fifty four patients were male, 52 female. Underlying diagnosis was lymphoma in 30, and solid tumors other than lymphoma in 72. The mean ANC was 436.8/uL (range, 0-1000); 4 patients had an ANC of <10/uL. Twenty-three patients (22.5%) died of complications related to NF. There was no statistical difference in therapeutic outcome between tumor types, i.e. lymphoma versus non-lymphoma (p=0.521), PS (p=0.438), sex (p=0.099), depth of neutropenia (p=0.162), or time intervals from visiting ER to starting antibiotic therapy (p=0.414). Age was important prognostic factor in therapeutic outcome. The median age in fatal cases was 62 years where as that of non-fatal cases was 54 (p=0.016). Bacteremia was documented in 19 patients among whom 10 (53%) died. Mortality was significantly higher in patients with blood culture proven bacteria than patients whose blood culture yielded no organism (p=0.013).

**Conclusion:** The review of NF seen at our ER showed substantial mortality especially in elderly patients. Given the rising age in cancer diagnosis as well as therapeutic intervention, higher mortality rate associated with chemotherapy induced NF in elderly patients needs further study seeking better way to reduce NF and risk of death.

**Keywords:** Lymphoma, Solid tumor, Chemotherapy, Neutropenia, Fever, Bacteremia, Mortality

**Pathophysiological Role of Hormones and Cytokines in Cancer Cachexia**

**Hyun Jung Kim**, **Han Jo Kim**, **Kyoung Ha Kim**, **Se Hyung Kim**, **Mi-Sun Jeong**, **Geum Ha Jang**, **Sang-Cheol Lee**, **Sang Byung Bae**, **Chan Kyu Kim**, **Nam Su Lee**, **Kyu Taek Lee**, **Sung Kyu Park**, **Jong Ho Won**, **Hee Sook Park**, **Dae Sik Hong**

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**Background:** Cancer-induced cachexia is the most common paraneoplastic syndrome and is recognized as an indicator of poor prognosis. Cancer cachexia differs from starvation, but has not been fully elucidated. We investigated the role of fasting hormones (adiponectin, ghrelin, and leptin) and pro-inflammatory cytokines (TNF-α, IFN-γ, and IL-6) in cancer patients.

**Methods:** Hormones (ghrelin, adiponectin, and leptin) and cytokines (TNF-α, IFN-γ, and IL-6) were measured by
ELISA or RIA in lung cancer and colorectal cancer patients before the administration of cancer therapy, and measurements were repeated every 2 months for a total of three times. Statistical analysis was performed to determine the relationship of hormone and cytokine levels to weight change.

**Results:** From June 2006 to August 2008, 42 patients (19 with colorectal cancer and 23 with lung cancer) were enrolled. In total, 21 patients were included in the cachexia group and the others served as a comparison group. Similar distributions in terms of age, diagnosis, and levels of hemoglobin (Hb), CRP, glucose, and insulin were observed in both groups, but the cachectic patients included more males than females, and these patients had lower albumin levels. No significant difference in the initial adiponectin, ghrelin, TNF-α, IFN-γ, or IL-6 level was observed between groups, although leptin was significantly lower in cachectic patients than in the comparison group (15.3±19.5 vs. 80.9±99.0 pg/ml, p=0.007). Hormone and cytokine levels did not differ between colorectal and lung cancer patients. During the follow-up, the patients who showed a >5% weight gain had higher ghrelin levels (weight gain vs. no change vs. weight loss: 1223.1±383.7 pg/m, 594.2±218.1 vs. 654.3±218.1 pg/ml, p=0.007) after 6 months and lower cytokine levels (TNF-α, IFN-γ, and IL-6) than the control, but the differences were not statistically significant. Patients exhibiting elevated IL-6 levels typically showed a weight loss >5% after 6 months. **Conclusion:** A blunted adiponectin or ghrelin response to weight loss may contribute to cancer cachexia. Patients with initially higher levels of IL-6 experienced weight loss. After 6 months, those who had gained weight (>5%) showed elevated ghrelin levels, and therefore a clinical trial examining the effect of ghrelin treatment on cancer cachexia may be warranted.

**Keywords:** Cancer cachexia, Hormone, Cytokine

Sunitinib for Unselected Korean Patients with Advanced Renal Cell Carcinoma: A Comparable Efficacy with Different Toxicity Profiles

**Background:** Although various prognostic factors have been proposed to predict survival in terminally ill cancer patients, accurate prognostication is still a challenging task for oncologists. The objective of this study was to evaluate whether the time interval between diagnosis of advanced cancer and cessation of active anti-cancer treatment (ATP; active treatment period) can predict survival in terminally ill cancer patients.

**Methods:** We prospectively evaluated 79 patients with advanced (recurrent or metastatic) cancer who were determined as terminal stage, namely cessation of active anti-cancer treatment and transition to palliative care, by at-

**Results:** This population includes 82.6% of clear cell, and 28.8% of treatment naive patients. The progression free survival (PFS) and overall survival were 8.2 months and 23.1 months, respectively. With median 5 cycles of sunitinib treatment, the ORR was 34.1% (n=45), and 44.7% (n=59) exhibited SD. Reasons for disconomination were disease progression (n=99 [75.0%]) and treatment related toxicity (n=10 [7.6%]). The mean and median relative dose intensity (RDI) were 82.0% (SD=±14.20) and 84.1% (range 48.0-100), respectively. The most frequent adverse events were thrombocytopenia (75.0%), neutropenia (70.5%), anemia (69.7%), and stomatitis/mucositis (66.7%). Grade 3-4 adverse events were also very high, being thrombocytopenia (37.8%), neutropenia (29.5%), anemia (21.9%), and HFS (15.2%). Grade 3-4 thrombocytopenia was peaked during cycle 1-4 (15-23.1%), and gradually reduced in accordance with the RDI adjustment. Low BSA (OR 4.2, 95% CI 1.2-13.8, p=0.02), and previously treated status (OR=3.1, 95% CI 1.3-7.4, p=0.01) were highly predictable for grade 3-4 toxicities. Based on these results, a nomogram predicting 12 month-PFS probability was constructed with the 0.675 of concordance index.

**Conclusion:** For unselected Korean advanced RCC patients, sunitinib demonstrates favorable efficacy and manageable toxicities. Though more frequent and somewhat different toxicity profiles, adequate dose modification and careful follow up enables comparable treatment outcomes. Based on different toxicity profiles, further trials to optimize the dose/schedule are warranted.

**Keywords:** Renal cell cancer, Sunitinib, Toxicity

Interval between Diagnosis of Advanced Cancer and Cessation of Active Anti-cancer Treatment Can Predict Survival in Terminally Ill Cancer Patients

**Background:** Although various prognostic factors have been proposed to predict survival in terminally ill cancer patients, accurate prognostication is still a challenging task for oncologists. The objective of this study was to evaluate whether the time interval between diagnosis of advanced cancer and cessation of active anti-cancer treatment (ATP; active treatment period) can predict survival in terminally ill cancer patients.

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**Poster Presentation**

**P-71**

Interval between Diagnosis of Advanced Cancer and Cessation of Active Anti-cancer Treatment Can Predict Survival in Terminally Ill Cancer Patients

**Yu Jung Kim, June Koo Lee, Won-Suk Choi, Jin Hyun Park, Hee Jun Kim, Keun-Wook Lee, Se-Hoon Lee, Jee Hyun Kim, Dong-Wan Kim, Jong Seok Lee, Yung-Jue Bang, Dae Seog Heo**

Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Korea

**Background:** Although various prognostic factors have been proposed to predict survival in terminally ill cancer patients, accurate prognostication is still a challenging task for oncologists. The objective of this study was to evaluate whether the time interval between diagnosis of advanced cancer and cessation of active anti-cancer treatment (ATP; active treatment period) can predict survival in terminally ill cancer patients.

**Methods:** We prospectively evaluated 79 patients with advanced (recurrent or metastatic) cancer who were determined as terminal stage, namely cessation of active anti-cancer treatment and transition to palliative care, by at-
Employment Status and Work-Related Difficulties among Family Members of Terminally Ill Patients Compared with the General Population

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Background: Although caregiving to patients with terminal illness has been known to be a stressful burden to family members, little attention has been focused on their work-related problems. We aimed to investigate employment status and work-related difficulties of family caregivers with terminal cancer patients, comparing with the general population.

Methods: Using structured questionnaires, we assessed the employment status and work-related difficulties of family caregivers of 481 cancer patients determined by physicians to be terminally ill, from 11 university hospitals and the National Cancer Center in Korea.

Results: Among 381 family caregivers of terminal cancer patients (response rate, 87.6%), 169 (43.9%) were not working before cancer diagnosis, but currently 233 (63.7%) were not working. Compared with the general population (36.5%), the percentage of not working among the family caregivers was higher (OR=2.39; 95% CI=1.73-3.29). A major reason for not working was to provide assistance to the patients (71.6%). 40.6% of those who continually working and 32.3% of those who not working family members reported fatigue. Caregivers with old age, those who were female, those with a lower household income, and those caring for patients with a low performance status were not working at a more significant rate.

Conclusion: Family caregivers of terminal cancer patients suffer job loss and severe work-related difficulties, probably due to caregiving itself and to easy fatigue. We need to develop supportive programs to overcome the burden of caregivers of the terminally ill.

Keywords: Terminal cancer patient, Caregiver, Employment status, Work-related difficulty

Ondansetron Induced Extrapyramidal Reactions

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Nausea and vomiting are troublesome side effects of cytotoxic drug. Ondansetron is a selective serotonin (5-HT3) receptor antagonist used frequently to prevent and treat chemotherapy induced emesis. It is claimed to lack direct blocking action on the dopaminergic system; therefore, it was considered to be free of extrapyramidal symptoms (EPS). However, ondansetron associated EPS had been reported on several occasions. We describe an unusual presentation of ondansetron induced EPS characterized by carpopedal spasm, oromandibular dystonia. A 76-year-old female was diagnosed with chronic lymphocytic leukemia. She was treated with chlorambucil/prednisolone (chemotherapy) and ondansetron tablets (8 mg) were prescribed for nausea. She took ondansetron 8 mg orally for nausea and the next day the patient developed twisting of the right corner of the mouth (right hemi-facial spasm/oromandibular dystonia). Her hands were in a flexed and fisted position and their legs were in plantar flexion (carpopedal spasm). Computed tomographic scans of head, arterial blood gas analysis, and electrolyte analyses were normal. Chlorpheniramine 4 mg and diazepam 10 mg were administered intravenously, all symptoms of EPS resolved without sequelae within the first day. The symptoms did not recur after ondansetron was stopped.

Keywords: Ondansetron, Spasm
2009년 제9차
한국임상암학회 학술대회

인쇄: 2009년 11월 16일
발행: 2009년 11월 21일

발행인: 방영주
편집인: 임호영, 류백렬

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