Results: A total of 22 patients, 18 males and 4 females with a median age of 60 years old (54−82), 2/19/1 in PS 0/1/2 were enrolled between Dec. 2006 and Sep. 2008. All patients had received first line chemotherapy including S-1 and second line including irinotecan. Patients received median of 4 (range 1−12) cycles of treatment. Reasons for discontinuation were progression in 18 and withdrawal in 4. Grade 3 adversed events included neutropenia in 3 (14%), anemia in 1 (4%), appetite loss in 1 (4%). Overall response rate was 14%, disease control (PR+SD) rate was 77%, median TTF was 79 days, median PFS was 78 days, median overall survival don't reach.
Conclusions: A weekly regimen of paclitaxel was well tolerated and achieved a good disease control rate, and acceptable TTF relatively for advanced or recurrent GC. Although follow-up is ongoing on survival.

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Neoadjuvant chemotherapy followed by transthoracic resection for locally advanced carcinoma of the esophagus: a randomized study

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Background: A prospective trial was undertaken to investigate whether the chemotherapy followed by surgery results in increase of overall survival in patients with resectable thoracic esophageal cancer.
Material and Methods: 90 previously untreated patients with stage $T_{3-4}N_{0-1}M_0$, $T_{1-2}N_1M_0$ resectable esophageal cancer admitted to our center between March 2001 and December 2006. Patients were allocated either to two 3-day cycles of FLEP consisting of cisplatin 80–100 mg/m^2, day 1; etoposide 100 mg/m^2, leukovorine 20 mg/m^2 and 5-fluorouracil 500 mg/m^2, days 1−3; 21 days apart, followed by surgical resection (Ch-S group, n = 45), or resection alone (S group, n = 45). Patients' characteristics (tumor stage and histology, coexisting disorders, demographic data) were well balanced between the two treatment groups. Chemotherapy was completed in 42 patients. Four weeks after completion of chemotherapy or admission, patients were operated on. Transthoracic extended 2 or 3-field esophagectomy with intrapleural esophago-gastrostomy through I. Lewis approach was performed in 44 patients of Ch-S group and in all cases of S group.
Results: All patients but one had squamous cell cancer, one had adenocarcinoma. Complete response was observed in 4 patients (8.8%), partial response in 27 (60%), progression of disease in 3 patients (6.7%), and no change in 11 patient (24.5%) of Ch-S group. Eight patients had grade 3−4 neutropenia. There were no other serious manifestations of toxicity and no preoperative toxic deaths.
Resections were R0 in 39 patients in Ch-S group and 28 in S group (p = 0.06). Postoperative complications were reported in 53.3% Ch-S and 48.9% S patients (p = 0.7). Overall 3-year and 5-year survival rates were 39.8% and 28.5% in the S group; 62.9% and 40.4% in the Ch-S group (p = 0.08). 5-year disease-free survival benefit achieved statistical significance: 17.6% versus 32.7% (p = 0.04).
Conclusion: Two cycles of preoperative chemotherapy with 5-fluorouracil, cisplatin, leucovorin and etoposide followed by extended esophagectomy improve disease free survival of patients with resectable thoracic esophageal cancer.

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High-dose versus standard-dose radiation therapy in combined modality therapy for esophageal cancer

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Background: To compare the survival, local control, and toxicity of combined-modality therapy using high-dose (63 Gy) versus standard-dose (54 Gy) radiation therapy for the treatment of patients with esophageal cancer.
Materials and Methods: From January 1996 to July 2007, a total of 207 patients treated with concurrent chemoradiotherapy were analyzed. Of the 207 patients, 65 received $\leqslant$54 Gy (standard dose group) and 142 received $\geqslant$59.4 Gy (high dose group). The median doses in the standard and high dose groups were 54 Gy (range, 45−54 Gy) and 63 Gy (range, 59.4−70 Gy), respectively. The superior and inferior borders of the initial radiation field were 5 cm beyond the primary tumor. The superior and inferior borders of the boost field were decreased to 2 cm beyond the tumor. The median dose to the initial field was 36 Gy (range, 30.6−41.4 Gy) for both groups. Cisplatin and 5-fluorouracil were administrated to 85% of the patients, and the other patients received 5-fluorouracil mono-chemotherapy.
Results: There were no significant differences in patients' age, sex, pathology, and histological grade between the two groups. But Stage I-II patients were significantly higher in standard dose group (41% versus 19%). The median disease progression free survival and overall survival in all patients were 13 months and 24 months, and no significant differences were found between the two groups. But complete responses were higher in the high dose group (68% versus 33%, p = 0.04). Two-year local control rate was significantly higher in high dose group (75% vs. 64%, p = 0.05). No significant treatment related late toxicities were observed in both groups.
Conclusion: High dose group showed comparable survivals and higher complete response rate and local control rate without increasing toxicity compared to standard dose group while patients with advanced stage were higher in the high dose group.

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Outcomes of advanced gastric cancer in younger patients aged 45 years or less treated with first-line combination chemotherapy

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Background: The current study was performed to determine whether younger age is an independent prognostic factor among AGC patients receiving first-line chemotherapy and to evaluate how age relates to other known prognostic parameters.
Methods: The records of 1843 AGC patients who were consecutively treated with first-line combination chemotherapy at Samsung Medical Center (Seoul, Korea) between 2000 and 2007, including 570 patients aged 45 years or younger, were retrieved from a prospective cancer chemotherapy database.
Results: In the younger group, there were significantly more bone metastases, ascites, poor performance status, low albumin, elevated alkaline phosphatase, and resections that were non-curative than in the older patients. Progression-free survival (PFS) and overall survival (OS) was shorter in younger patients (PFS, 4.2 months; OS, 7.1 months) than in older ones (PFS, 4.9 months; OS, 8.4 months). Nonetheless, younger age did not show an independent association with PFS or OS. Stratified analyses showed that younger age was related with poor outcome in the subgroups of good performance status and no bone metastasis.
Conclusion: When matched for other prognostic factors, the prognosis of younger AGC patients receiving first-line combination chemotherapy does not differ from that of older patients. The poor survival of younger patients may be attributed to the association with other adverse prognostic factors.

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Updated long-term outcomes and failure pattern in patients with resectable esophageal cancer receiving one cycle of induction chemotherapy (capecitibine, cisplatin) followed by concurrent chemoradiation

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Background: Previously, we performed phase II study of one cycle of induction chemotherapy with capecitabine and cisplatin followed by concurrent chemoradiotherapy (CRT) in patients (pts) with resectable esophageal cancer (ASCO 2005 abstract 4063). We expanded the study population and analyzed the long-term results and pattern of treatment failure.
Material and Methods: From March 2003 to December 2006, a total of 106 pts with stage II/III resectable esophageal squamous cell carcinoma were enrolled. Patients received one cycle of induction chemotherapy (cisplatin 60 mg/m^2, D1, capecitabine 1000 mg/m^2 bid, D1−14) and followed by radiotherapy (46 Gy, 2 Gy/fraction) concurrent with weekly chemotherapy (cisplatin 30 mg/m^2, D1, 8, 15, 22, capecitabine 800 mg/m^2 bid, 5 days/week) during the entire course of radiation. Surgery was performed 4−6 weeks after completion of radiation therapy.
Results: The median age including 98 men (93%) was 63 years (range, 45−74). One hundred two pts completed concurrent CRT. Overall clinical response in the intention-to-treat population after CRT was 93% (99 pts) including 48% (51 pts) of complete response (CR) rate. Seventy eight pts (74%) underwent surgical resection. Pathologic CR was achieved in

55 pts (52%). Most common grade 3/4 toxicity was thrombocytopenia (10%) followed by neutropenia (9%) and vomiting (3%). With a median follow-up duration of 46 months (range 20−67), 3-year progression-free survival (PFS) and overall survival (OS) rates were 45% and 48%. The median PFS and OS were 27 months [95% confidence interval (CI) 17−37] and 34 months [95% CI 22−47]. In a subgroup analysis, the pts who achieved clinical CR after concurrent CRT showed a significant better PFS (15 vs 56 months, p = 0.002 by log-rank) and OS (20 vs 56 months, p = 0.005 by log-rank) than those not. Treatment failure with loco-regional progression or distant metastases was observed less frequently in pts with clinical CR than in pts without clinical CR (20% vs 44%, p = 0.007 for overall failure rate; 10% vs 30%, p = 0.014 for failure rate due to distant metastases).
Conclusions: This treatment regimen is well tolerated, effective for resectable esophageal squamous cell carcinoma with excellent major clinical response rate and survival outcomes.

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Discordant ErbB2 status between primary gastric carcinomas and metastatic/recurrent carcinomas

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Background: To evaluate the ErbB2 status in primary gastric carcinoma (GC) and secondary (metastatic or recurrent) lesions, 614 cases of GC were examined.
Materials and Methods: Primary GC consisted of 325 cases resected over one year at one institute, and 3 different areas were examined per case. Paired samples of primary GC and metastasis from 124 cases of regional lymph node metastasis, 65 cases of synchronous distant metastasis and 61 cases of metachronous distant metastasis were collected. Paired samples of 39 cases of primary GC and local recurrence were also collected. IHC to detect ErbB2 protein was performed using HercepTest Kits, and ErbB2 immunostaining was scored using the 4 grade system. Dual color Vysis kits (PathVysion) were used for FISH analysis of ErbB2.
Results: Similar to breast cancer, IHC and FISH results were well correlated in GC, except for IHC 2+ cases. None of the IHC 0 cases showed ErbB2 amplification, and all IHC 3+ cases showed ErbB2 amplification. About one-sixth of IHC 2+ cases showed ErbB2 amplification. FISH analysis of secondary lesions showed that positive conversion (no amplification in primary GC but amplification in secondary carcinoma) occurred in 2.1%, and negative conversion (amplification in primary GC but no amplification in secondary carcinoma) occurred in 0.7%. Heterogeneous amplification was found in 2.5% of primary GC, while 2.8% of the secondary lesion showed the different amplification result with that of primary GC. Among the cases with ErbB2 amplification, heterogeneous amplification was found in 23% (8/35) of primary GC, while different amplification result between primary and secondary lesions was found in 19.5% (8/41).

Table 1. ErbB2 IHC and FISH result in paired primary and secondary GC

	Amplification (%)	
IHC	Primary lesion	Secondary lesion
0	0/126 (0.0)	0/113 (0.0)
1+	2/83 (2.4)	1/83 (1.2)
2+	10/57 (17.5)	10/65 (15.4)
3+	23/23 (100)	28/28 (100)
Total	35/289 (12.1)	39/289 (13.5)

Conclusion: ErbB2 amplification was found in 12.1% of primary GC and 13.6% of secondary lesion. IHC and FISH results correlated very well in primary and secondary GCs, similar to breast cancer. There is heterogeneity within each GC tissue and also between primary and secondary lesions. Discordant amplification between primary and secondary carcinomas may represent heterogeneous amplification in primary GC.

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Optimal treatment for superficial esophageal cancer: surgery or endoscopic therapy?

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Background: Interest in endoscopic therapies for superficial esophageal cancer has been increasing. The aim of this study was to clarify the optimal treatment strategy for superficial esophageal cancer, mucosal (Tis and T1a) and submucosal cancer (T1b), based on the results of surgical treatment.
Patients and Methods: Between 1986 and 2006, 139 patients (124 males and 15 females, median age 62 years) with a superficial esophageal cancer (129 with squamous cell carcinoma, 7 with adenocarcinoma, and 3 with others) underwent radical esophagectomy with extended lymphadenectomy. We reviewed the clinicopathologic results and postoperative survival of these patients.
Results: The depth of tumors resected were Tis in 5 patients, T1a in 32, and T1b in 102. Patients with Tis had no lymph node involvement. Three of the 32 patients with T1a cancer had lymph node involvement (9.4%). All of them had T1a cancer adjacent to the layer of muscularis mucosae. Forty-two (41.2%) of the 102 T1b cancer patients had nodal involvement (N1), and 13 had M1-lym (12.7%). The operative mortality was 0.7%, and the in-hospial mortality rate was 1.4%. The 5- and 10-year overall survival rate of the Tis and T1a cancer patients were 94.2% and 61.1%, and those of the T1b patients were 72.1% and 56.1%, respectively. One patient of the Tis and T1a cancer patients died of recurrent disease (2.7%), and 14 patients with T1b cancer died of recurrent disease (13.7%). Other co-occurring primary malignancy was presented in 51 patients (36.7%), and 17 patients died of this other malignancy. Cause of death in half of patients who survived more than 5 years was other malignancies. While there was no difference in the survival in patients with superficial esophageal cancer between N0 and N1, there was a significant difference in the survival between those with other primary malignancy and those without (p = 0.008).
Conclusions: Most of Tis and T1a esophageal cancer could be curatively treated by endoscopic treatment, such as EMR or ESD, while radical esophagectomy with lymph node dissection is necessary for patients with T1b cancer. Control of other primary malignancies is important to improve the survival of patients with superficial esophageal cancer.

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Phase II trial of S-1 for elderly patients (pts) over 75 years with advanced gastric cancer as first-line treatment (OGSG0404)

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Introduction: S1-based regimens are commonly used for advanced gastric cancer (AGC) in Japan. The usefulness of S-1 +CDDP in the treatment of AGC has been demonstrated by the SPIRITS phase III trials conducted in Japan. However, because over 75 years pts were excluded from this trial, the significance of S-1 based chemotherapy for elderly AGC pts is unclear. We therefore conducted a multicenter cooperative phase II study of S-1 monotherapy for AGC in elderly pts.
Methods: Between 11–2007 and 06–2008, elderly chemotherapy-naïve pts over 75 years with AGC were enrolled at 9 institutions. The primary endpoint was the response rate (RR; the Japanese Research Society for Gastric Cancer criteria or RECIST), and the secondary endpoints were safety, progression free survival (PFS) and overall survival (OS). S-1 (40−60 mg) was given twice daily. The starting dose was determined on the basis of body surface area (BSA) and the creatinine clearance value (Ccr), and courses of administration for 4 weeks followed by a 2-week rest period were repeated.
Results: 35 pts were enrolled: median age 78 (75−86), 21 M; 14 F. The RR was 14.3%, and the disease control rate was 57.1%: 0 CR; 5 PR; 15 NC; 10 PD; 5 NE. Median PFS was 95 days, and the median OS was 511 days, 1-year survival rate was 61.1%, Grade 3 or more adverse events consisted of anemia (9%), neutropenia (3.3%), anorexia (3.3%), and fatigue (6.6%) without no treatment-related death.
Conclusions: Our study indicates that S-1 is safe, well tolerated and mild active in elderly chemotherapy-naïve pts over 75 years with AGC.