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Impact of sequential lines of palliative chemotherapy in patients with recurrent/metastatic esophageal squamous cell carcinoma : A retrospective analysis of 107 patients in a single center

재발성, 전이성 식도 편평상피세포암 환자에서 치료 차수에 따른 고식적 항암치료의 중요성 : 단일 기관에서 107명 환자에 대한 후향적 분석

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Impact of sequential lines of palliative chemotherapy in patients with recurrent/metastatic esophageal squamous cell carcinoma : A retrospective analysis of 107 patients in a single center

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이 논문을 의학석사 학위 논문으로 제출함

2019 년 2 월

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Abstract

Background: Effective, tolerable treatment options are limited in case of recurrent/metastatic esophageal squamous cell carcinoma (ESCC). Efficacy data for palliative chemotherapy by the lines of chemotherapy are limited. We retrospectively analyzed progression-free survival (PFS) for each line of chemotherapy.

Materials and Methods: All 107 patients who began palliative chemotherapy at the Asan Medical Center for recurrent/metastatic ESCC from March 2015 to October 2017 were included, and grouped according to previous curative treatment; Groups A (previous chemoradiation alone, n=30), B (previous surgery alone, n=11), C (previous chemoradiation and surgery, n=30), and D (initially metastatic or de novo stage IV, n=36). Groups A, B, C (n=71(30+11+30); pretreated group) and Group D (n=36; treatment-naïve group) were reorganized according to treatment history. Overall response rate (ORR) and survival data were evaluated for each group, line of chemotherapy and chemotherapeutic regimen.

Results: Baseline characteristics of the pretreated and treatment-naive groups were comparable (exceptions: distant metastasis and TNM stage). ORR were 25.2%, 7.3%, and 3.4% in 1st, 2nd, and 3rd-line chemotherapy, respectively. Median PFS was 4.7, 2.0 and 2.2 months in 1st, 2nd, 3rd-line chemotherapy, respectively. The median OS (10.1 [95% CI, 7.3-12.9] months) was not significantly different between pretreated and treatment-naive groups (p=0.88). Previous surgery, good performance, ≥ 3 lines of chemotherapy, and low C-reactive protein level were linked to a significantly longer OS in multivariate analysis.

Conclusion: PFS declined rapidly with progress of lines of palliative chemotherapy. OS in treatment-naïve and pretreated groups was not significantly different. If tolerable, continuing advanced lines of chemotherapy may have survival benefit.

Keywords: Esophageal Neoplasms, Drug Therapy, Palliative Care

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Introduction

Esophageal cancer is the 8th most common cancer worldwide and the 6th most common cause of cancer-death according to Global Cancer Incidence, Mortality and Prevalence (GLOBOCAN) 2012 [1]. In Korea, the overall incidence of esophageal cancer is rising because of the aging of the Korean society [2]. In Korea, the predominant pathologic type of esophageal cancer is squamous cell carcinoma rather than adenocarcinoma [3,4].

Esophageal squamous cell carcinoma (ESCC) is a highly aggressive disease. Although surgery is mainstay of treatment in resectable ESCC, nearly 40% of patients are diagnosed with advanced (metastatic) disease, having a 5-year survival rate of less than 5-10% [2, 3]. Moreover, previous resectable cases have a high rate of recurrence, with an expected median survival of 24 months and a 5-year survival rate of less than 30% [4]. The poor outlook of ESCC is reflected in its high mortality-to-incidence rate ratio of 0.83 [5].

In locally advanced disease, to improve outcome of surgery alone and to control subclinical micrometastasis, neoadjuvant/adjuvant and definite chemoradiation have been established since the 1990s [6]. Combination of 5-fluorouracil (5-FU) or capecitabine (Xeloda®) plus cisplatin for definite concurrent chemoradiation therapy (CCRT) has been showing a high efficacy rate [7].

In case of metastatic/recurrent ESCC, the availability of effective and tolerable treatment options is limited [8]. In these cases, palliative chemotherapy is one of the treatment options to control cancer-related symptoms and to prolong survival [9]. According to current knowledge, a combination of 5-FU and cisplatin (FP) is the most effective and commonly used chemotherapeutic regimen, with approximate response rate of 30% in advanced esophageal cancer [6, 10]. A combination regimen comprised of capecitabine and cisplatin (XP) regimen also has proven efficacy and is being used as a 1st-line chemotherapeutic regimen [11, 12]. Due to lack of large randomized trials, there is currently no consensus on the standard regimen for 2nd-line chemotherapy in relapsed or refractory cases [4, 8, 13]. Several small studies have shown that for refractory disease, the taxane regimen is effective as a single agent [3, 8, 13-16], or in combination with platinum-based chemotherapy [14]. Docetaxel has a 16 % response rate and gives an 8.1-month median survival in 2nd-line

chemotherapy [6, 15]. Paclitaxel is also effective as 2nd-line [10, 16, 17]. Besides, combination regimens with irinotecan have been evaluated in several studies [17, 18]. Current research trends on palliative chemotherapy are increasingly focused on immune-oncologic agents. For more than 3rd-line chemotherapy, data ┣ on its efficacy or survival are insufficient. Therefore, advanced lines of chemotherapy are often replaced by best supportive care in some centers.

Esophageal cancer easily metastasizes to distant site because of unique anatomical features of esophagus including absence of serosa, presence of the periesophageal adventitia that connects it with the mediastinum structures, multiple arterial resources, abundant venous plexuses that drain into large vessels, and a complex lymphatic network [19]. Initially metastatic (or de novo stage 4) ESCC may have different biology compared to that of recurrent or progressed ESCC after curative treatment; palliative chemotherapy is indicated in such cases. However, comparison between efficacy data of palliative chemotherapy in two groups has not been well delineated. In addition, data evaluating clinical effectiveness of sequential lines of chemotherapy, especially that of advanced lines of chemotherapy are not sufficient in patients with ESCC.

In this study, we retrospectively analyzed 107 ESCC patients who received palliative chemotherapy in real world setting. Progression-free survival (PFS) for each line of chemotherapy and effectiveness of advanced lines of chemotherapy were evaluated. We also compared the efficacy of palliative chemotherapy between de novo stage IV (treatment-naïve) group and pretreated group (previously administered curative treatment including CCRT, surgery, or both CCRT and surgery).

Materials and Methods

Patients and Data Collection

This study was reviewed and approved by the institutional review board (IRB) of Asan Medical Center. Informed consent was not written, because it was retrospective study. After approval, we completed review of databases for all patients who started palliative chemotherapy for histologically confirmed ESCC between March, 2015 and October, 2017 in Asan Medical Center, Seoul, South Korea (n=107). Patients who were originally scheduled to undergo CCRT, but could only be administered induction chemotherapy because of poor compliance or rapid disease progression were not included (N=, since the chemotherapy was not administered as palliative treatment. Endoscopic submucosal dissection (ESD) was classified as surgery.

A standard data form was created to retrieve information about baseline characteristics of patients, tumor characteristics including TNM stage, laboratory data at the time of starting 1st-line palliative chemotherapy, previous treatments (surgery, chemoradiation, and chemotherapy), and follow-up data. The American Joint Committee on Cancer (AJCC) cancer staging manual: the 7th edition was applied for TNM staging [20]. Types of chemotherapeutic regimen, start and end date of chemotherapy, causes of stopping chemotherapy, response to chemotherapy, and the date of progression were reviewed from 1st-line to 3rd-lines of chemotherapy. Patients who underwent more than three lines of chemotherapy were also documented.

Patients were classified into four groups according to previous treatment; Group A (previous chemoradiation alone, n= 30 patients), B (previous surgery alone, n= 11 patients), C (previous chemoradiation and surgery, n=30 patients), and D (de novo stage IV, n=36 patients) (Figure 1). Pretreated group A, B, and C (n=71=30+11+30) and the treatment-naïve group D (de novo stage IV group, n=36) were reorganized according to previous history of exposure to curative treatment.

Chemotherapeutic regimens were categorized into 5 groups, as follows: a 5-FU or capecitabine plus cisplatin (FP/XP) group, a taxane (docetaxel or paclitaxel alone) group, an irinotecan plus cisplatin group, an immunotherapy group, and ‘other regimen’ group. Patients

treated with an immuno-oncologic agent alone or in combination with a cytotoxic agent (seven patients with 1st-line, seven patients with 2nd-line, and four patients with 3rd-line treatment) were classified into an 'immunotherapy group'.

Overall response rate (ORR), survival data (progression-free survival [PFS] and overall survival [OS]) were compared according to the groups defined above, chemotherapeutic agents and lines of chemotherapy. The previous CCRT group (A, C) and de novo stage IV group (D) were also compared to see both the effect of previous chemotherapy included in CCRT and the effect of disease status (recurrent or progressive disease after curative treatment or initially metastatic disease). Response to chemotherapy was evaluated every 2-3 cycle by RECIST (Response Evaluation Criteria in Solid Tumors) Criteria version 1.1. The possibility of proceeding to subsequent chemotherapy, compliance to chemotherapy and prognostic factors for OS were also evaluated.

Compliance to each line of chemotherapy was calculated by using the following formula: [1 – (patients who stopped chemotherapy due to toxicity, follow-up loss, poor performance, or patient's request and patients who were not evaluated/all patients who underwent chemotherapy)]x100 (%). PFS was defined as the length of time from the date of initiation of the line of chemotherapy to the date of disease progression or death from any cause, whichever occurred first. OS was defined as the length of time from the beginning of the 1st-line chemotherapy to the date of death from any cause.

After review and discussion, possible prognostic factors including age, sex, type of previous treatment, distant metastasis, chemotherapeutic regimen, tumor location, size at diagnosis, grade of differentiation, family history, Eastern Cooperative Oncology Group performance status (ECOG PS), neutrophil-to-lymphocyte ratio (NLR), C-reactive protein (CRP) level, albumin level, and compliance were selected for evaluation [21-23]. The cutoff value of NLR was 5 and that for CRP was 5 mg/dL [24].

In our clinical experience, among ESCC patients, about 3% are "outliers" with reference to the standard predicted prognosis, and survive longer than others receiving palliative chemotherapy. We identified 7 patients (6.5% of all patients) who survived longer than others and summarized their clinical characteristics.

Statistical analysis

Descriptive statistics were used for describing the baseline characteristics of patients. Pearson's chi-square, Man-Whitney, Fisher's exact tests and one-way ANOVA were used for comparison of discrete data as required. Survival was estimated using the Kaplan-Meier method, and the log-rank test was used to determine the significance of any differences in survival curves. All tests were two-sided, and $p < 0.05$ was considered statistically significant. Cox-regression analysis were used for univariate and multivariate analysis to evaluate prognostic factors. The SPSS 25.0 software (IBM SPSS Inc., Chicago, IL) was used for all analyses.

Results

Baseline characteristics

The median age was 63 years (range, 38-83). Baseline characteristics at the beginning of palliative chemotherapy were well-balanced between the treatment-naïve and pretreated groups (Table 1). Only TNM stage at the time of diagnosis and distant metastasis at the beginning of palliative chemotherapy were significantly different from each group ($p<0.001$ for both analysis). This implied that the disease was more advanced in patients of the treatment-naïve group. Patients in treatment-naïve group were administered palliative chemotherapy as initial treatment because all patients in this group had initially metastatic or de novo stage IV disease; patients in the pretreated group had a previously history of CCRT or surgery because the majority of (50 of 71, 70.4%) patients in this group initially had stage 1-3 disease.

Chemotherapeutic regimen

The number of patients for each line of chemotherapy was as follows; 1st-line, 107; 2nd-line, 55; and 3rd-line, 29. Partially due to Korean insurance regulations, the most commonly prescribed chemotherapeutic regimens for each line were FP/XP, taxane, and irinotecan plus cisplatin, for 1st- 2nd-, and 3rd-line chemotherapy, respectively. All patients who started 1st-line palliative chemotherapy with taxane (n=22) were in the pretreated group, especially in previous CCRT group (A, C), because they had already received FP/XP as part of CCRT. Therefore, chemotherapeutic agents were significantly different between the pretreated and treatment-naïve groups ($p=0.001$).

In the present study, programmed cell death protein 1 (PD-1) inhibitors including pembrolizumab, nivolumab, atezolizumab and tislelizumab were used as immunotherapeutic agents. In most patients, pembrolizumab was administered as a single agent as part of the Keynote 181 or the Keynote 180 trial or was combined with cytotoxic chemotherapeutic agents as part of the Keynote 590 study (NCT03189719, NCT02559687, and NCT02564263, respectively). Nivolumab was administered as part of ONO4538-24 trial (NCT02569242). Since nivolumab was partially approved in Korea for 2nd-line or beyond 2nd-line therapy in

ESCC in January 2018, two patients received nivolumab without enrollment in any clinical trial. Atezolizumab was administered with cytotoxic chemotherapeutic agents (FOLFOX) as part of the GO30140 study (NCT02715531). Tislelizumab was administered as part of the BGB-A317 trial (NCT03430843).

Response to chemotherapy

Overall response rates as per lines of chemotherapy were as follows; 1st-line, 25.2%; 2nd-line, 7.3%; and 3rd-line, 3.4%. Response rate to 1st-line chemotherapy was higher in treatment-naïve group than in the pretreated group, but the difference was not statistically significant (30.6% vs. 22.5%, p=0.48, Table 2). There may be estimation errors in the treatment-naïve group because the response rate was not evaluated in a large number (13.9%) of patients. When the previous chemoradiation group (A, C) and the de novo stage IV group (D) were compared, a similar result was obtained (30.6% vs. 18.3%, p=0.21). In subgroup analysis, the response rate of group B (previous surgery alone) was significantly higher than that of group A (previous chemoradiation alone) (45.5% vs. 10.0%, p=0.02).

The FP/XP regimen elicited the highest response rate (29.3%, 22/75 patients) among the 1st-line regimens. The response rate was not significantly different between the FP/XP and taxane regimens (p=0.41). Because of the small number of the patients, it was not feasible to compare response rates among other regimens. All 5 patients who responded to 2nd- and 3rd-line chemotherapy were in the taxane group (ORR; 4/37 patients in 2nd-line with taxane, 1/5 patients in 3rd-line with taxane).

Survival analysis; progression-free survival

Median PFS was 4.7 [95% CI, 4.0-5.4], 2.0 [1.8-2.2] and 2.2 [1.8-2.6] months for 1st-, 2nd-, and 3rd-line chemotherapy, respectively. There was no significant difference in median PFS after 1st-line chemotherapy (PFS1) between the treatment-naïve and pretreated group (p=0.86). When the previous chemoradiation group (A, C) and the de novo stage IV group (D) were compared, a similar result was obtained (p=0.53). When classified according to previous surgery (Group B, C vs. A, D), the median PFS1 in the previous surgery group was significantly longer than that in the group without surgery (5.2 [95% CI, 3.3-7.1] vs. 4.2 [3.7-

4.7] months, p=0.03) with a median follow-up duration of 13.7 [95% CI, 11.5-15.9] months. In subgroup analysis, the median PFS1 was superior in group B (previous surgery alone) than it was in the other groups. Median PFS was not reached in group B, while it was 3.6 [95% CI, 2.0-5.2], 5.0 [4.4-5.5] and 5.0 [3.3-6.8] months in group A, C, and D, respectively (p=0.005, 0.053, and 0.02, respectively).

Median PFS1 in the FP/XP group was numerically longer than that in the taxane group, which was not statistically significant (5.0 [95% CI, 4.1-5.8] vs 2.6 [0.0-5.3] months, p=0.08). Median PFS1 in the lower NLR (< 5) group was significantly longer than that in the higher NLR (≥ 5) group (5.0 [95% CI, 4.2-5.9] vs. 3.2 [1.7-4.6] months, p<0.001). Also, the median PFS1 in the lower CRP (< 5mg/dL) group was significantly longer than that in the higher CRP (≥ 5mg/dL) group (4.8 [95% CI, 4.0-5.5] vs. 1.1 [0.4-1.8] month, p<0.001). The median PFS1 in patients with ECOG PS 0 was significantly longer than in patients with ECOG PS 1 (8.1 [95% CI, 4.2-12.1] vs. 4.4 [3.8-5.0] months, p=0.049). Also, the median PFS1 in patients with ECOG PS 1 was longer than in patients with ECOG PS 2 (4.4 vs. 3.2 [0.3-6.0] months, p=0.87), though the difference was not statistically significant. Initial stage at diagnosis, distant metastasis at the initiation of palliative chemotherapy, and tumor location (upper, middle or lower) at diagnosis did not show significant association with PFS after 1st-line chemotherapy.

In PFS analysis after 2nd-line chemotherapy, there was no significant difference between the pretreated and treatment-naïve groups (p=0.67). When the previous chemoradiation group (A, C) and the de novo stage IV group (D) were compared, a similar result was obtained (p=0.55). With a median follow-up of 8.4 months [95% CI, 8.3-8.5 months], the median PFS after 2nd-line chemotherapy (PFS2) in patients with FP/XP as 2nd-line regimen was significantly longer than that in the taxane and 'other regimen' groups (6.7 [95% CI, 6.5-6.9] vs. 1.8 [1.6-2.1], and 2.0 [0.8-3.1] months, p=0.006 and 0.02, respectively). However, the numbers of patients in the FP/XP and 'other regimen' group were small (n=6 and 4, respectively). The median PFS2 in the lower CRP (<5 mg/dL) group was significantly longer than that in the higher CRP (≥5 mg/dL) group (2.0 [95% CI, 1.8-2.2] vs. 0.8 months, p=0.001). However, the number of patients with the higher CRP group was also small (n=2). NLR did not show a significant association with median PFS2 (p=0.93). Patients who showed a PFS1 longer than the median

PFS1 showed a significantly longer PFS2 (2.4 [95% CI, 0.6-4.3] vs. 1.5 [0.8-2.2] months, p=0.03, Figure 2).

In PFS analysis after 3rd-line chemotherapy, there was no significant difference between pretreated group and treatment-naïve group. When previous chemoradiation group (A, C) and the de novo stage IV group (D) were compared, a similar result was obtained. Likewise, the median PFS was not significantly different among chemotherapeutic regimens. Longer PFS1 than the median PFS1 and a PFS2 longer than the median PFS2 did not show significant association with a longer PFS3.

Survival analysis; overall survival

The median OS was 10.1 month [95% CI, 7.3-12.9] with a median follow-up duration of 18.9 [95% CI, 16.1-21.7] months. Although the pretreated group showed a longer median OS than did the treatment-naïve group, the difference was not significant (10.1 vs. 9.1 months, p=0.88). When the previous chemoradiation group (A, C) and the de novo stage IV group (D) were compared, the median OS of both group were almost same (9.0 vs. 9.1 months, p=0.72). On the other hand, median OS of patients who underwent surgery (group B, C) was longer than that of patients who did not undergo surgery (group A, D) (12.0 [95% CI, 8.8-15.2] vs 7.4 [4.6-10.1] months, p=0.04). In subgroup analysis, the median OS of group B (previous surgery alone) was the longest. In contrary, median OS of group A (previous CCRT alone) was the shortest. The median OS of group A was significantly shorter than that of group B and C (7.0 [95% CI, 5.5-8.5] vs. 14.6 [4.9-24.3] and 10.9 [7.3-14.4] months, p=0.03 and p=0.04, respectively).

Patients who received FP/XP as initial chemotherapy showed significantly longer median OS than those who received taxane (10.9 [95% CI, 7.9-13.8] vs. 5.4 [1.2-9.5] month, p=0.003, Figure 3A). However, all patients who received taxane as the 1st-line regimen belonged to the previous CCRT group (A, C). To exclude the effect of previous chemotherapy as a probable confounding factor, we compared OS between the FP/XP and taxane groups only in the previous CCRT group. There was still a significant difference in median OS between the two groups (10.8 [95% CI, 9.6-12.0] vs. 5.4 [1.2-9.5] months, p=0.006, Figure 3B). There were no significant differences among median OS values of the 2nd- and 3rd-line chemotherapeutic

regimen groups.

The median OS after palliative chemotherapy in lower NLR (< 5) group was significantly longer than that in the higher NLR (≥ 5) group (10.9 [95% CI, 9.0-12.8] vs. 5.5 [3.9-7.2] months, p<0.001). Also, the median OS after 1st-line chemotherapy in the lower CRP (< 5) group was significantly longer than that in the higher CRP (≥ 5) group (10.6 [95% CI, 8.0-13.3] vs 2.1 [1.1-3.1] months, p<0.001).

Among patients whose response to 1st-line palliative chemotherapy was progressive disease (PD), those who received 2nd-line chemotherapy showed significantly longer median OS than the patients who did not receive the therapy (11.2 [95% CI, 9.9-12.6] vs 3.5 [1.2-5.9] months, p<0.001, Figure 4A). Among patients whose response to 2nd-line chemotherapy was PD, the patients who received 3rd-line chemotherapy showed significantly longer median OS than patients who did not receive the therapy (12.4 [95% CI, 11.1-13.7] vs. 8.4 [1.0-15.8] months, p=0.04, Figure 4B). Among patients whose response to 3rd-line chemotherapy was PD, those who received 4th-line chemotherapy showed longer median OS than those who did not receive the therapy, though the difference was not statistically significant (17.1 vs. 12.4 months, p=0.38).

Having a PFS longer than the median PFS after 1st (PFS1) and 2nd-line palliative chemotherapy (PFS2) was significantly associated with a longer OS (PFS1; 17.1 [95% CI, 12.7-21.4] vs. 5.1 [4.3-5.9] months, p<0.001, PFS2; 26.6 [9.0-44.3] vs 10.8 [9.8-11.9] months, p=0.001, Figure 2, 5A, and 5B). However, the association was not statistically significant in 3rd-line chemotherapy (PFS3; 17.1 [17.0-17.2] vs 11.7 [10.5-13.0], p=0.09, Figure 5C).

The median OS in patients with ECOG PS 0 was significantly longer than that in patients with ECOG PS 1 (21.0 [95% CI, 13.4-28.5] vs. 8.5 [5.4-11.6] months, p=0.02). Also, the median OS in patients with ECOG PS 1 was longer than that in patients with ECOG PS 2 (8.5 vs. 2.9 [1.0-4.9] months, p=0.13), though the difference was not statistically significant. On the other hand, the median OS in patients with middle-located cancer was significantly longer than that in patients with widely-located (upper-middle, middle-lower, or upper-middle-lower esophagus) cancer (12.8 [95% CI, 10.0-15.5] vs. 7.4 [4.5-10.3] months, p=0.03). Initial stage at diagnosis, distant metastasis at initial palliative chemotherapy, concomitant cancer, tumor size at diagnosis (≤3 or >3 cm), family history, grade of differentiation (well, moderate or

poor), and the year when 1st-line chemotherapy was started did not show significant association with OS after palliative chemotherapy.

In general, the ORR rapidly declined with the advancing lines of chemotherapy in both treatment-naïve and pretreated groups (Table 2). However, the slope of declining ORR curve was steeper in the treatment-naïve group. Consequently, the ORR of 3rd-line chemotherapy in the treatment-naïve group was 0 %, although that of the pretreated group was maintained at 6.3%. A similar trend was observed in PFS according to advancing lines of chemotherapy. As a result, although the ORR and PFS of 1st-line chemotherapy in the pretreated group tended to be inferior to those of the treatment-naïve group, the OS of the pretreated group was similar to that of the treatment-naïve group. Compliance with 2nd-line chemotherapy was better than that with 1st-line chemotherapy in each group. It is suggested that only patients with good compliance could proceed to subsequent line of chemotherapy.

Prognostic factor analysis and outliers

On univariate analysis of OS, age, sex, previous curative treatment, distant metastasis at the beginning palliative chemotherapy, initial stage, ECOG performance status, NLR, CRP, albumin level, 1st-line chemotherapeutic regimen, location and size of tumor at diagnosis, grade of differentiation, family history, total lines of chemotherapy, and compliance at 1st-line chemotherapy were evaluated. Among them, previous surgery (hazard ratio (HR) 0.61, 95% CI, 0.38-0.98, p=0.04), ECOG performance status (ECOG 1 vs. 0; HR 3.77, 95% CI, 1.18-12.11, p=0.03, ECOG ≥ 2 vs. 0; HR 6.54, 95% CI, 1.75-24.45, p=0.005), high NLR (≥ 5 vs. < 5, HR 2.42, 95% CI, 1.40-4.19, p=0.002), high CRP (≥ 5 vs. < 5 mg/dL, HR 8.75, 95% CI, 4.35-17.63, p<0.001), taxane as 1st-line chemotherapeutic regimen (vs. FP/XP, HR 2.26, 95% CI 1.31-3.92, p=0.004), and total lines of chemotherapy (≥3 vs. 1; HR 0.52, 95% CI, 0.30-0.89, p=0.02) were significantly associated with the median OS (Table 4). Of these factors, previous surgery (HR 0.60, 95% CI, 0.36-1.01, p=0.05), ECOG performance status (ECOG 1 vs. 0; HR 4.72, 95% CI, 1.43-15.65, p=0.01, ECOG ≥ 2 vs. 0; HR 5.07, 95% CI, 1.28-20.10, p=0.02), high CRP (HR 1.29, 95% CI, 1.14-1.46, p<0.001), and total lines of chemotherapy (≥3 vs. 1; HR 0.52, 95% CI, 0.30-0.89, p=0.005) remained as significant predictive factors for longer OS on multivariate analysis.

We summarized clinical characteristics of the seven outlier patients who showed the longest OS (data not shown). No patient met the criteria for improved survival for all the four significant prognostic factors as per multivariate analysis. Two patients met the criteria for three factors, four patients for two factors, and one patient for one factor.

Proportion of patients that undergo further chemotherapy (PPF)

The proportion of patients that could undergo further chemotherapy after failure of chemotherapy is summarized in Table 3. The proportion of patients advanced to 4th-line chemotherapy among all patients who received palliative chemotherapy was higher in treatment-naïve group than it was in the pretreated group, though this difference was not statistically significant (p=0.058). When the previous CCRT group (A, C) and the de novo stage IV group (D) were compared, the proportion who advanced to 4th-line chemotherapy was significantly higher in the de novo stage IV group (Relative risk [RR] 2.5, 95% CI, 1.7-3.9, p=0.01). However, all patients who received taxane as the 1st-line regimen belonged to the previous CCRT group. To exclude effect of chemotherapeutic regimen as probable confounding factor, we compared the proportion of patients who advanced to 4th-line chemotherapy, between previous CCRT and de novo stage IV group only in FP/XP group. There was no significant difference between the two groups (p=0.17). In subgroup analysis, the proportion of patients who advanced to 4th-line chemotherapy was significantly lower in group A than in group B and D (p=0.07 and p=0.03, respectively).

When evaluated by chemotherapeutic regimen, among the patients whose disease was PD after 1st-line chemotherapy, the proportion of patients who advanced to 2nd-line chemotherapy was significantly higher in the FP/XP group than that in the taxane group (RR 1.6, 95% CI, 1.1-2.5, p=0.007). In addition, all nine patients who proceeded to 4th-line chemotherapy were in the FP/XP group. To exclude previous CCRT as a factor, we compared the proportion of patients who advanced to 2nd-line chemotherapy between the FP/XP and taxane groups only among those who received previous CCRT (A, C), and found a significant difference in these proportions (RR=2.7 [95% CI, 1.1-6.5], p=0.008). The proportion of patients who advanced to 4rd-line chemotherapy among all patients who received palliative chemotherapy was higher in the FP/XP group than in the taxane group, though this difference was not statistically

significant (p=0.11).

Time to progression/recurrence

In the pretreated group, time from last curative treatment to progression or recurrence (TTP), which led to palliative chemotherapy, was evaluated (Table 5). Median TTP was 4.3 months in group A (previous CCRT alone), 11.6 months in group B (previous surgery alone), and 5.7 months in group C (previous CCRT and surgery), and these TTP values were significantly different from each other (p<0.001). In post hoc analysis, a significant difference was observed between the median TTP values of group A and B, and that of group B and C (p<0.001, p=0.001, respectively), which implies that CCRT may be associated with a risk of early progression or recurrence.

Proportions of patients whose TTP was within 6 months were 76.7%, 45.5%, and 50.0% in group A, B and C, respectively (Table 5). In the early progression/recurrence group (TTP<6 months), the median PFS of 1st-line palliative chemotherapy was significantly shorter than that of the late progression/recurrence group (4.1 [95% CI, 3.3-4.9] vs. 6.2 [0.8-11.6] months, p=0.003). A similar result was obtained when the PFS was compared between patients with TTP<1 year and TTP≥1 year (p=0.02). The median OS of 1st-line chemotherapy was shorter in the early progression/recurrence group (TTP<6 months), but the difference was not statistically significant (p=0.20). A similar result was obtained when the median OS of 1st-line chemotherapy was compared between TTP<1 year and TTP≥1 year (p=0.26). TTP within 6 months or 1 year was not significantly associated with using the taxane regimen as 1st-line palliative chemotherapy (p=0.28, p=0.73, respectively).

Progression or recurrence pattern was also assessed. Systemic/local progression/recurrence ratio was 1.0, 2.5 and 1.25 in group A, B and C, respectively, and demonstrated a relative tendency for systemic recurrence in the surgery group and for local progression/recurrence in the CCRT group. The PFS1 was significantly longer in patients with systemic progression than it was in patients with both local and systemic progression (6.1 [95% CI, 2.2-10.0] vs. 2.9 [1.1-4.7] months, p=0.02). PFS1 was longer in patients with local progression than it was in patients with both local and systemic progression, but this difference was not statistically significant (5.0 vs. 2.9 months, p=0.058). Progression or recurrence pattern was not significantly

associated with OS.

Discussion

This study described recent trends and progress of palliative chemotherapy for ESCC in the largest tertiary medical center of South Korea. Since the multidisciplinary team approach with surgery, chemoradiation and palliative chemotherapy for esophageal cancer been adopted over 20 years in our center, this data would reflect real-world data by lines of chemotherapy in recurrent/metastatic ESCC. Thus, our findings will be helpful for clinicians managing esophageal cancer, including thoracic surgeons and radiation oncologists in addition to oncologists.

To our knowledge, this is the first study comparing survival of palliative chemotherapy between a pretreated group who previously underwent curative treatment and a treatment naïve-group in metastatic/recurrent ESCC. In a study that assessed prognostic factors for post-recurrence survival in patients who underwent curative esophagectomy for esophageal cancer, neoadjuvant chemotherapy or chemoradiation was not significantly associated with survival [25]. However, the study did not include treatment-naïve patients, and only 16% of patient underwent palliative chemotherapy. In the present study, the treatment- naïve group showed a slightly higher ORR for 1st-line chemotherapy and longer median PFS1 than did the pretreated group or the previous CCRT group. Decreased sensitivity to chemotherapy because of previous CCRT and relative chemosensitivity of initially metastatic ESCC (treatment-naïve group) may explain this observation. In addition, some clinicians chose taxane as the 1st-line chemotherapeutic regimen instead of FP/XP, because response to FP/XP which was administered in previous CCRT was not satisfactory, or the time to progression after CCRT was short. However, ORR and PFS according to advancing lines of chemotherapy declined more rapidly in the treatment-naïve group than in the pretreated or previous CCRT group. Consequently, the OS of the pretreated group was similar to that of the treatment-naïve group. Although both initially metastatic disease and recurrent or progressive disease after curative treatment are indication of palliative chemotherapy, disease burden and whether distant metastasis presents may differ from each other. Since 26.8% of patients did not have distant metastasis at initiation of palliative chemotherapy in the pretreated group, it might take more time to progress enough to cause mortality than in the

patients with initially metastatic disease. In short, despite decreased sensitivity to chemotherapy in the pretreated group or in the previous CCRT group, OS after palliative chemotherapy was similar in both the pretreated and the treatment-naïve groups because of relatively advanced disease status in patients belonging to the treatment-naïve group.

Previous studies have insisted that neoadjuvant CCRT plus surgery was better than definitive CCRT alone in terms of OS and local recurrence [7, 26]. Thus, surgery with or without neoadjuvant/adjuvant CCRT has been recommended over definite CCRT alone, if the disease is operable and the patient is able to tolerate surgery. In this study, group B (previous surgery only) was superior to group A (previous CCRT only) in terms of TTP, ORR, PPF (4^{th}- line chemotherapy), PFS1, and OS after palliative chemotherapy. Because it was a retrospective study, possible selection bias cannot be ruled out. It is thus possible that the baseline characteristics may have been favorable to the surgery group; additionally, the number of patients in group B was small. However, in multivariate analysis for OS, previous surgery was an independent prognostic factor despite the small number of patients. This result implies that definite local control with surgery may influence patient's survival even after the patient's disease progressed to advanced/recurrent setting.

In the present study, the ORR of the FP/XP regimen as 1^{st}-line chemotherapy in ESCC was 29.3%, which is consistent with that reported by previous studies [3, 14]. The median OS was10.9 months in the FP/XP group in 1^{st}-line chemotherapy, which was slightly longer than the OS reported by previous study (6-10 months). In addition, the FP/XP regimen as 1^{st}-line chemotherapy showed a significantly longer OS than did taxane. Although the FP/XP combination regimen, in comparison with the taxane regimen in 1^{st}-line palliative chemotherapy was not an independent prognostic factor in multivariate analysis for OS, the 'p' value was 0.053, which could be significant with a larger number of patients. FP/XP is a standard regimen for 1^{st}-line palliative chemotherapy in ESCC; however, studies directly comparing the FP/XP and taxane regimens as 1^{st}-line chemotherapy are lacking; the probable reason for this is that single-agent taxane is usually administered as 2^{nd}-line chemotherapy after a 5-FU based regimen. As mentioned earlier, all patients who received taxane regimen as the 1^{st}-line palliative chemotherapeutic regimen received the FP/XP regimen in previous CCRT, and the efficacy of CCRT with FP/XP turned out to be poor. Thus, patients who used

taxane as 1st-line regimen could not use FP/XP as the 2nd-line regimen while patients who received FP/XP as the 1st-line chemotherapy could use taxane regimen as the 2nd-line regimen, followed by an irinotecan regimen as 3rd-line regimen. Since the choice of chemotherapeutic regimen was more limited in taxane group, proportion of patients that underwent 2nd-line and 4th-line chemotherapy was lower in the FP/XP group than in the taxane group in TTP analysis. Thus, in multivariate analysis for OS, advanced line of chemotherapy was an independent prognostic factor while the 1st-line regimen did not achieve statistical significance. Narrower choice of further chemotherapeutic regimen might be a reason that OS was significantly shorter in the taxane group than in FP/XP group, although the PFS and ORR showed no significant difference.

In 2nd-line chemotherapy, taxane showed 10.8% of ORR, which was consistent with previous studies (5-20%). Additionally, it showed 4.9 months of median OS (from beginning of 2nd-line palliative chemotherapy), which was a bit shorter than previous studies (5-6 months).

In the present study, the efficacy of immunotherapeutic agents was relative inferior (in 1st-line chemotherapy, ORR; 14.3%, median PFS; 6.8 months, and median OS; 7.2 months) than it was in previous studies. In the KEYNOTE-028 study, pembrolizumab was active in pretreated ESCC with programmed death-ligand 1 (PD-L1), showing a partial response rate of 29.4% [27]. Since only few patients (n=7/107 in 1st-line chemotherapy) received immunotherapeutic agent in this study, further studies are needed to assess efficacy of immunotherapeutic agent in ESCC. Nowadays, immunotherapeutic agent is under active investigation in ESCC worldwide.

In this study, among the patients whose response to 1st or 2nd-line palliative chemotherapy was PD, those who received 2nd or 3rd-line chemotherapy showed significantly longer median OS than did those who did not receive the therapy. Likewise, among the patients whose response to 3rd-line chemotherapy was PD, those who received 4th-line chemotherapy showed longer median OS than did the patients who did not received the therapy, but the difference was not statistically significant. Although this was a retrospective analysis and there was a possibility that patients with good compliance and performance status could undergo subsequent chemotherapy, in multivariate analysis for OS including these factors,

continuing beyond 2nd-line chemotherapy was an independent prognostic factor. Thus, continuing sequential line of palliative chemotherapy in tolerable patient is important to prolong survival.

Despite recent developments in chemotherapy, especially introduction of immunotherapy and advances in palliative care, survival was not significantly prolonged compared to that reported by previous studies [11]. Thus, breakthroughs in palliative chemotherapy remain an urgent issue.

The main prognostic factors for OS were found to be previous surgery, ECOG performance status, CRP level, and total lines of chemotherapy. This result was in line with that reported by previous studies [22, 23, 28]. However, tumor size at diagnosis, grade of differentiation, and family history of esophageal cancer which were identified as prognostic factors after esophagectomy in previous study were not significantly associated with OS in this study [29]. With regard to patients who were outliers with reference to prognosis, prognostic factor identified in this study could not explain all of the reasons for the longer survival in these outliers; there were many other patients with comparable statuses of prognostic factor as the outliers, but did not survive as long. One possible cause of the extraordinarily long survival in three patients is that there may have been small, or even non-measurable tumor burden when beginning palliative chemotherapy. Two other patients were able to tolerate successive chemotherapy. Although their disease progressed after chemotherapy, these patients survived and proceeded to the subsequent line of chemotherapy. One patient showed a robust response to 2nd-line docetaxel (PFS 22.0 months). Treatment response in the last one patient was not as robust, but the patient survived after PD at 2nd-line chemotherapy, probably due to slow progression of the tumor. Hidden factors such as velocity of progression of tumor, individual susceptibility and tolerability for each chemotherapeutic agent may have played a role in survival in these patients. Further biomarker studies and genetic assessments are necessary to identify such factors.

Inflammation is a known major driver for the development and progression of cancer [29]. CRP was traditionally associated with prognosis of various types of cancer including esophageal cancer. Likewise, NLR is an index of systemic inflammation, and tends to be

higher in patients with an upper gastrointestinal malignancy, and in those with advanced, aggressive disease requiring chemotherapy [24]. Our study revealed that high baseline NLR and CRP were significantly associated with poorer PFS and OS. In multivariate analysis, CRP was an independent prognostic factor for OS in ESCC patients on palliative chemotherapy.

The present study had several limitations. It was a retrospective study without control group and included heterogeneous patients. The clinical settings and chemotherapeutic regimens of patients were also varied. Thus, the number of patients in some patient groups was too small to conduct statistical analysis. In addition, although all patients who started palliative chemotherapy at the center were included, there could be selection bias in each patient group. To develop better chemotherapeutic regimens and combined treatment strategies, matched prospective studies or randomized trials with larger patients are needed in the future.

Esophageal cancer remains a great challenge to oncologists. In this study, previous history of chemoradiation was not significantly associated with OS. Since PFS rapidly declines with advancement of line of chemotherapy, incorporation of highly effective treatment modalities in early line treatments is crucial in the management of recurrent/metastatic ESCC. In addition, if the patient is able to tolerate chemotherapy, advanced lines of chemotherapy may prolong survival. Trials evaluating newer chemotherapeutic agents and combination of agents may help identify potentially more active and better-tolerated systemic regimens. Discovering biomarkers related to response or resistance to chemotherapy should also be continued to refine the use of existing therapies for ESCC.

Conclusion

PFS and patients undergoing subsequent treatment declined rapidly with advancement of line of CTx. Thus, wise incorporation of effective treatment modalities in earlier lines is crucial in the management of ESCC. OS in the previous CCRT and de novo stage IV groups was not significantly different. If the patient is tolerable, advanced lines of chemotherapy helps prolong survival.

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Table 1. Patient characteristics at the time of starting palliative chemotherapy for esophageal squamous cell carcinoma

Characteristic	Pretreated group (n=71, %)	Treatment-naïve group (n=36, %)	*P*
Median age, years (range)	63, (38-83)	65, (42-79)	
≤ 65	44 (62.0)	19 (52.8)	.41
> 65	27 (38.0)	17 (47.2)	
Gender			
Male	66 (93.0)	35 (97.2)	.66
Female	5 (7.0)	1 (2.8)	
ECOG performance status			
0-1	61 (85.9)	31 (86.1)	.73
≥ 2	6 (8.5)	4 (11.1)	
Not evaluated	4 (5.6)	1 (2.8)	
Median NLR, (range)	2.90, (0.83-17.8)	2.45 (0.85-7.99)	
≤ 5	59 (83.1)	29 (80.6)	.79
> 5	12 (16.9)	7 (19.4)	
CRP			
≤ 5	61 (85.9)	30 (88.9)	.50
> 5	9 (12.7)	2 (5.6)	
Not evaluated	1 (1.4)	4 (11.1)	
Albumin			
≤ 3.5	33 (46.5)	22 (61.1)	.22
> 3.5	38 (53.5)	14 (38.9)	

Initial TNM stage (at diagnosis)			
1	12 (16.9)	0 (0)	**<.001**
2	8 (11.3)	0 (0)	
3	30 (42.3)	0 (0)	
4	20 (31.0)	36 (100)	
Not evaluated	1(1.4)	0 (0)	
Distant metastasis at the time of starting palliative chemotherapy			
Yes			
No	52 (73.2)	36 (100)	**<.001**
	19 (26.8)	0 (0)	
Site of metastasis		Total; 88	
LN		48 (54.5)	
Lung		31 (53.2)	
Liver		21 (23.9)	
Bone		20 (22.7)	
Others[a]		21 (23.9)	
Concomitant cancer[b]		Total; 18	
Stomach cancer		7 (38.9)	
Colorectal cancer		3 (16.7)	
Lung cancer		3 (16.7)	
Thyroid cancer		2 (11.1)	
Others[c]		5 (27.8)	

ECOG, Eastern Cooperative Oncology Group; NLR, neutrophil lymphocyte ratio; TNM, tumor node metastasis; CRP, C-reactive protein; LN, lymph node

[a] Others include pleura, peritoneum, thyroid, chest wall, colon, skin, spleen, and pancreas.

[b] Any type of cancers which were diagnosed before and during palliative chemotherapy were took in.

[c] 'Others' include breast cancer, acute myeloid leukemia, hepatocellular carcinoma, prostate cancer, gallbladder cancer, and ureter cancer.

Table 2. Response, survival, compliance, and m/c chemotherapeutic agents by lines of palliative chemotherapy in study patients.

Lines of chemotherapy	ORR	PFS	OS	Compliance	m/c chemotherapeutic agent
1st-line (n=107)	25.2%	4.7 months	10.1 months	62.6%	FP/XP
2nd-line (n=55)	7.3%	2.0 months		67.3%	Taxane
3rd-line (n=29)	3.4%	2.2 months		55.2%	Irinotecan/cisplatin
	Treatment-naïve group (=De novo stage IV, N=36)				
1st-line (n=36)	30.6%	5.0 months	9.1 months	66.7%	FP/XP
2nd-line (n=23)	4.3%	1.9 months		73.9%	Taxane
3rd-line (n=13)	0%	2.1 months		53.8%	Irinotecan/cisplatin
	Pretreated group (N=71)				
1st-line (n=71)	22.5%	4.7 months	10.1 months	60.6%	FP/XP
2nd-line (n=32)	9.3%	2.0 months		62.5%	Taxane
3rd-line' (n=16)	6.3%	2.3 months		56.3%	Irinotecan/cisplatin

ORR; Overall response rate, PFS; progression-free survival, OS; overall survival, m/c; most common; FP/XP, 5-fluorouracil or capecitabine plus cisplatin

Table 3. The proportion of patients who could undergo further chemotherapy after failure of chemotherapy

	1st-line CTx	PD	2nd-line CTx	PD	3rd-line CTx	PD	Further CTx	Over 4th-line CTx /initial CTx
Number of patients (proportion of further CTx/PD, %)	107	78	55 (70.5)	43	29 (67.4)	18	10 (55.6)	8.8 %
Pretreated (Group A-C)	71	51	32 (62.7)	24	16 (66.7)	10	3 (30.0)	**4.2 %**
- Group A [a]	30	25	13 (52.0)	8	6 (75.0)	4	0 (0)	**0 %**
- Group B	11	4	3 (75.0)	3	2 (66.7)	2	2 (100.0)	**18.2 %**
- Group C	30	22	16 (72.7)	13	8 (61.5)	4	1 (25.0)	**3.3 %**
Treatment-naïve (Group D)	36	27	23 (85.2)	19	13 (68.4)	8	6 (75.0)	**16.7 %**
Chemotherapeutic regimen								
FP/XP	75	53	**45 (84.9)**	36	**26 (72.2)**	17	9 (**52.9**)	**12.0** %
Taxane	22	18	**7 (38.9)**	6	**2 (33.3)**	1	0 (0)	0 %
Immunotherapy	7	5	**1 (20.0)**	0	0 (-)	0	0 (-)	0 %
Others	3	2	**2 (100.0)**	1	**1 (100)**	0	0 (-)	0 %

CTx, chemotherapy; FP/XP, 5-fluorouracil or capecitabine plus cisplatin; PD, progressive disease

[a] Group A (previous chemoradiation alone), B (previous surgery alone), C (previous chemoradiation and surgery), and D (de novo stage IV).

Table 4. Prognostic factor analysis for overall survival.

Factors	Univariate analysis		Multivariate analysis	
	HR (95% CI)	***P* value**	**HR (95% CI)**	***P* value**
Age	0.999 (0.973-1.025)	0.922		
Female (vs. Male)	0.612 (0.223-1.685)	0.342		
Previous surgery	**0.607 (0.376-0.982)**	**0.042**	**0.600 (0.356-1.010)**	**0.05**
Previous chemoradiation	1.209 (0.769-1.902)	0.411		
Distant metastasis at starting palliative CTx	1.634 (0.859-3.110)	0.134		
Initial TNM stage; 1	Reference	0.569		
2	1.112 (0.313-3.943)	0.870		
3	1.781 (0.718-4.415)	0.213		
4	1.588 (0.676-3.731)	0.289		
ECOG : 0	Reference	**0.020**	Reference	**0.037**
1	**3.772 (1.175-12.110)**	**0.026**	**4.723 (1.426-15.647)**	**0.011**
≥ 2	**6.544 (1.751-24.451)**	**0.005**	**5.071 (1.279-20.102)**	**0.021**
NLR ≥ 5	**2.424 (1.401-4.194)**	**0.002**	1.610 (0.841-3.082)	0.151
Albumin ≤ 3.5	1.280	0.285		

	(0.814-2.015)			
CRP ≥ 5	**8.754 (4.348-17.625)**	**<0.001**	**1.294 (1.148-1.460)**	**<0.001**
Primary CTx regimen : FP/XP	Reference	**0.036**	Reference	
Taxane	**2.263 (1.306-3.922)**	**0.004**	1.791 (0.993-3.228)	0.053
Others	0.992 (0.241-4.083)	0.991		
Immunotherapy	1.304 (0.468-3.633)	0.611		
Tumor location; upper	Reference	0.252		
mid	0.694 (0.354-1.360)	0.287		
lower	0.872 (0.464-1.638)	0.669		
multiple	1.362 (0.674-2.750)	0.389		
Tumor size at diagnosis	1.090 (0.976-1.216)	0.127		
Grade of differentiation : well	Reference	0.414		
moderate	1.069 (0.425-2.690)	0.888		
poor	0.709 (0.251-2.001)	0.516		
Family Hx	1.147 (0.460-2.863)	0.768		

Lines of chemotherapy; 1	Reference	0.052	Reference	
2	0.695 (0.395-1.220)	0.205		
≥3	**0.520 (0.304-0.890)**	**0.017**	**0.414 (0.225-0.762)**	**0.005**
Good compliance to 1st line CTx (vs. bad)	0.680 (0.424-1.092)	0.111		

HR, hazard ratio; CI, confidence interval; NLR, neutrophil to lymphocyte ratio; CTx, chemotherapy; Hx, history; TNM, tumor node metastasis; ECOG, Eastern Cooperative Oncology Group; CRP, C-reactive protein; FP/XP, 5-fluorouracil or capecitabine plus cisplatin

Table 5. Time to progression/recurrence after previous concurrent chemoradiotherapy or surgery in esophageal squamous cell carcinoma.

	A: Previous CCRT alone (N=30, %)	**B: Previous surgery alone (N=11, %)**	**C: Previous CCRT and surgery (N=30, %)**	***P***
Median time to progression/recurrence, range (month)	**4.3**, 0-22.8	**11.6**, 1.3-129.0	**5.7**, 1.1-23.4	**<.001**
Progression/recurrence within 6 months	23 (76.7)	5 (45.5)	15 (50.0)	
Progression/recurrence within 1 year	27 (90.0)	5 (45.5)	24 (60.0)	
Progression/recurrent type				
Local alone	11 (36.7)	2 (18.2)	8 (26.7)	
Systemic alone	11 (36.7)	5 (45.5)	10 (33.3)	
Local and systemic	5 (16.7)	2 (18.2)	11 (36.7)	
Systemic/local ratio	1.0	2.5	1.25	

CCRT; Concurrent chemoradiation therapy

Figure 1. Classification of patients undergoing palliative chemotherapy according to previous treatment.

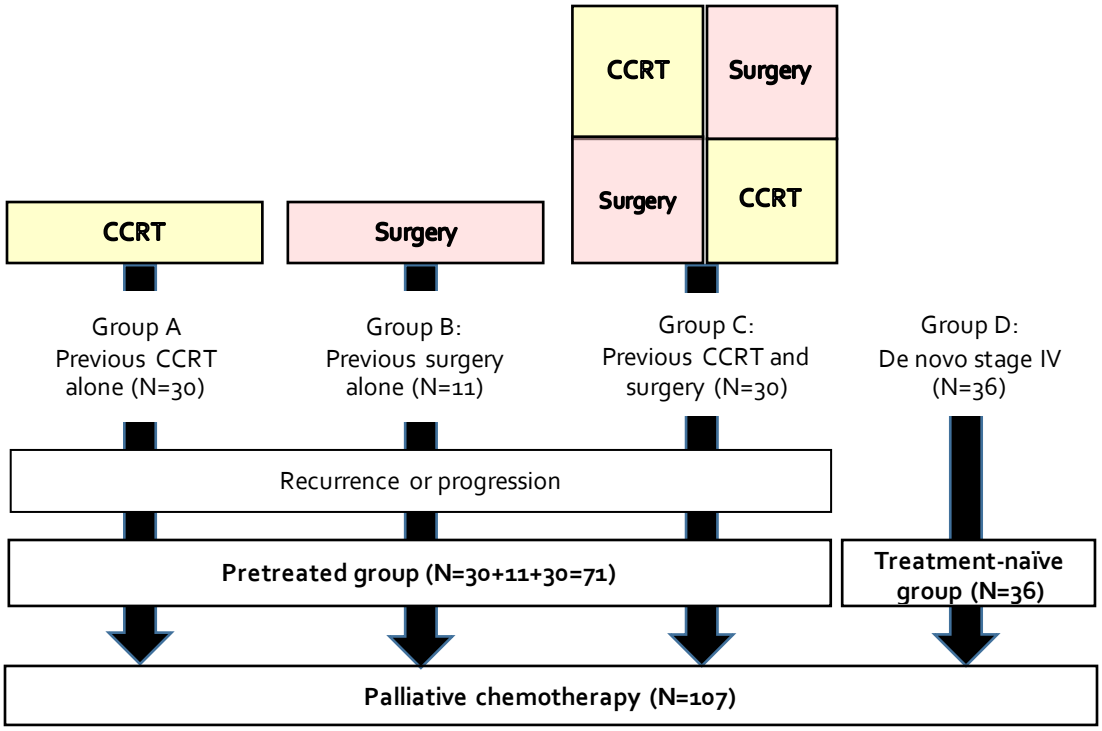
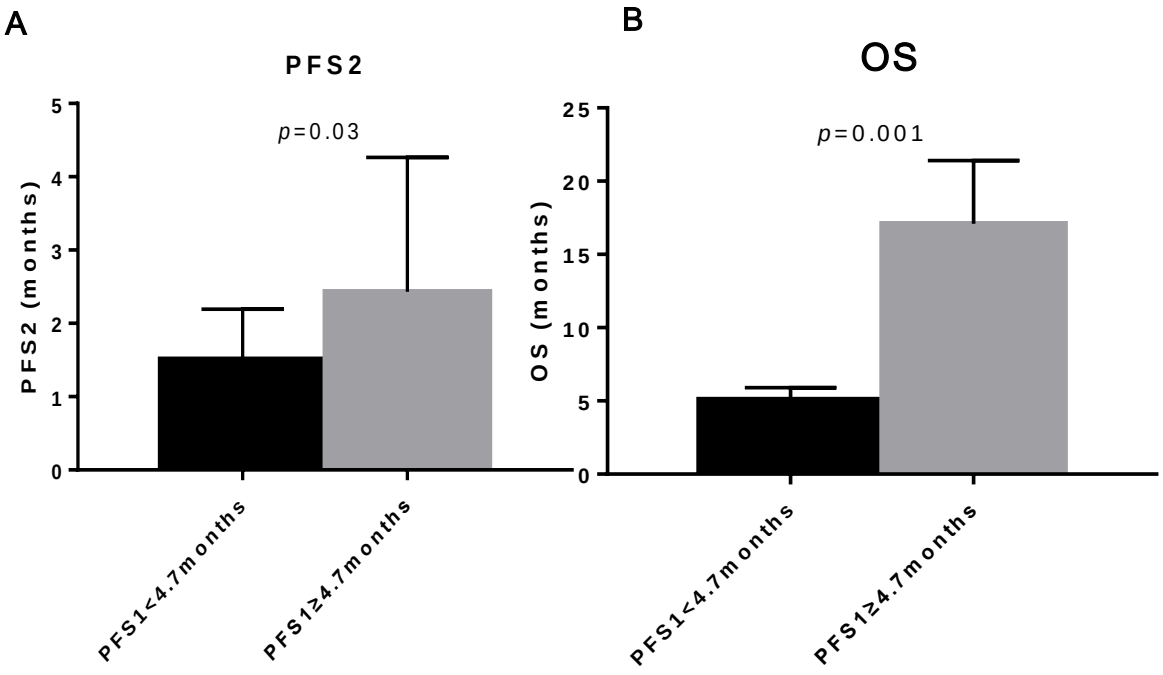


Figure 2. (A) PFS after 2nd-line chemotherapy (PFS2) and **(B)** OS in patients who showed shorter PFS1 than median PFS1 and in patients who showed longer PFS1 than median PFS1.



PFS1; Progression-free survival after 1st-line palliative chemotherapy

Figure 3. (A) Kaplan-Meier estimates of OS after palliative chemotherapy in esophageal squamous cell carcinoma, according to 1st-line chemotherapeutic regimens.

(B) Kaplan-Meier estimates of OS after palliative chemotherapy in esophageal squamous cell carcinoma, **especially in previous CCRT group,** according to 1st-line chemotherapeutic regimens (FP/XP vs taxane).

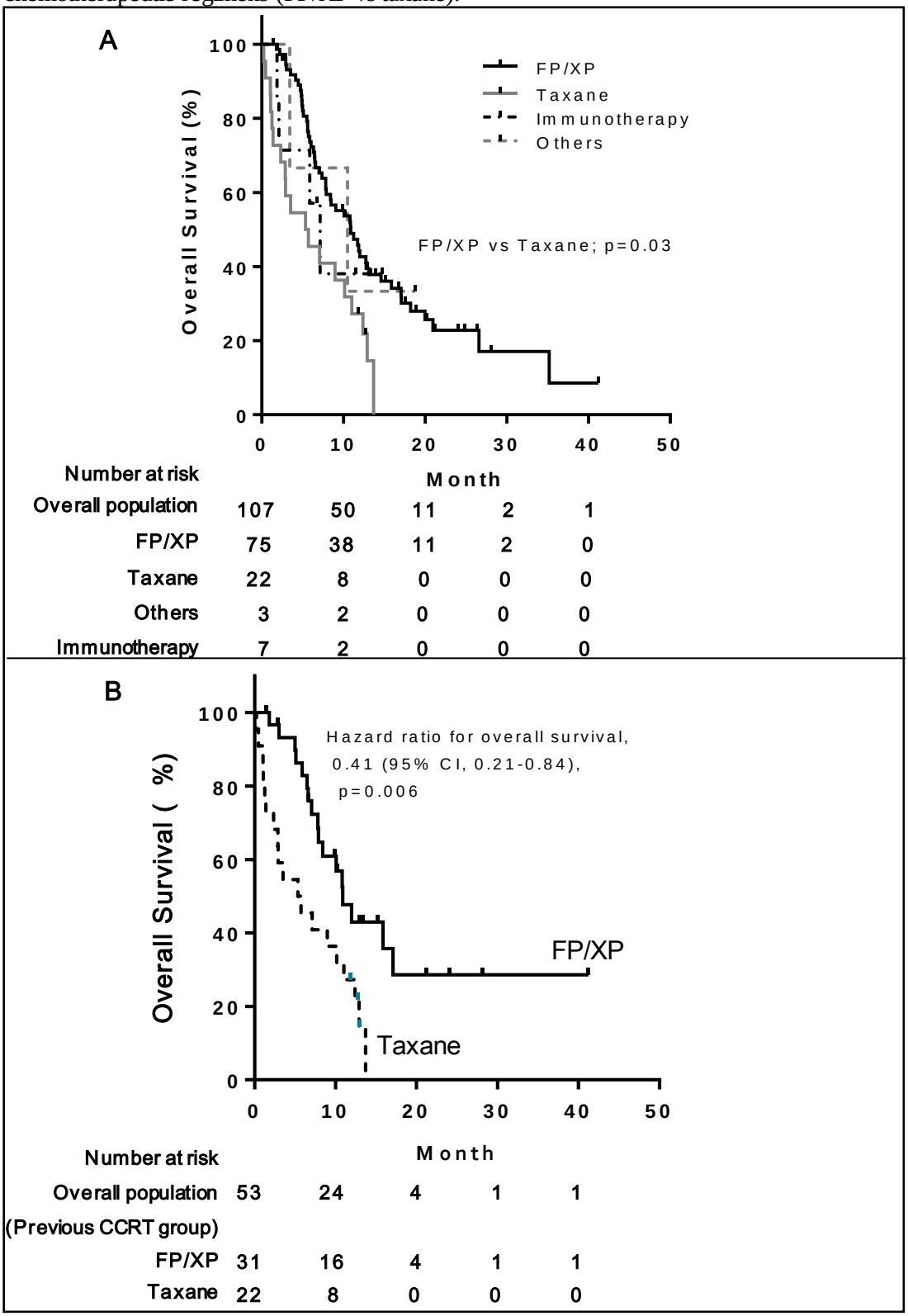


Figure 4. (A) Kaplan-Meier estimates of OS of patients whose diseases were PD after 1st-line palliative CTx in ESCC, according to whether 2nd-line chemotherapy was done.

(B) Kaplan-Meier estimates of OS of patients whose diseases were PD after 2nd-line palliative CTx in ESCC, according to whether 3rd-line chemotherapy was done.

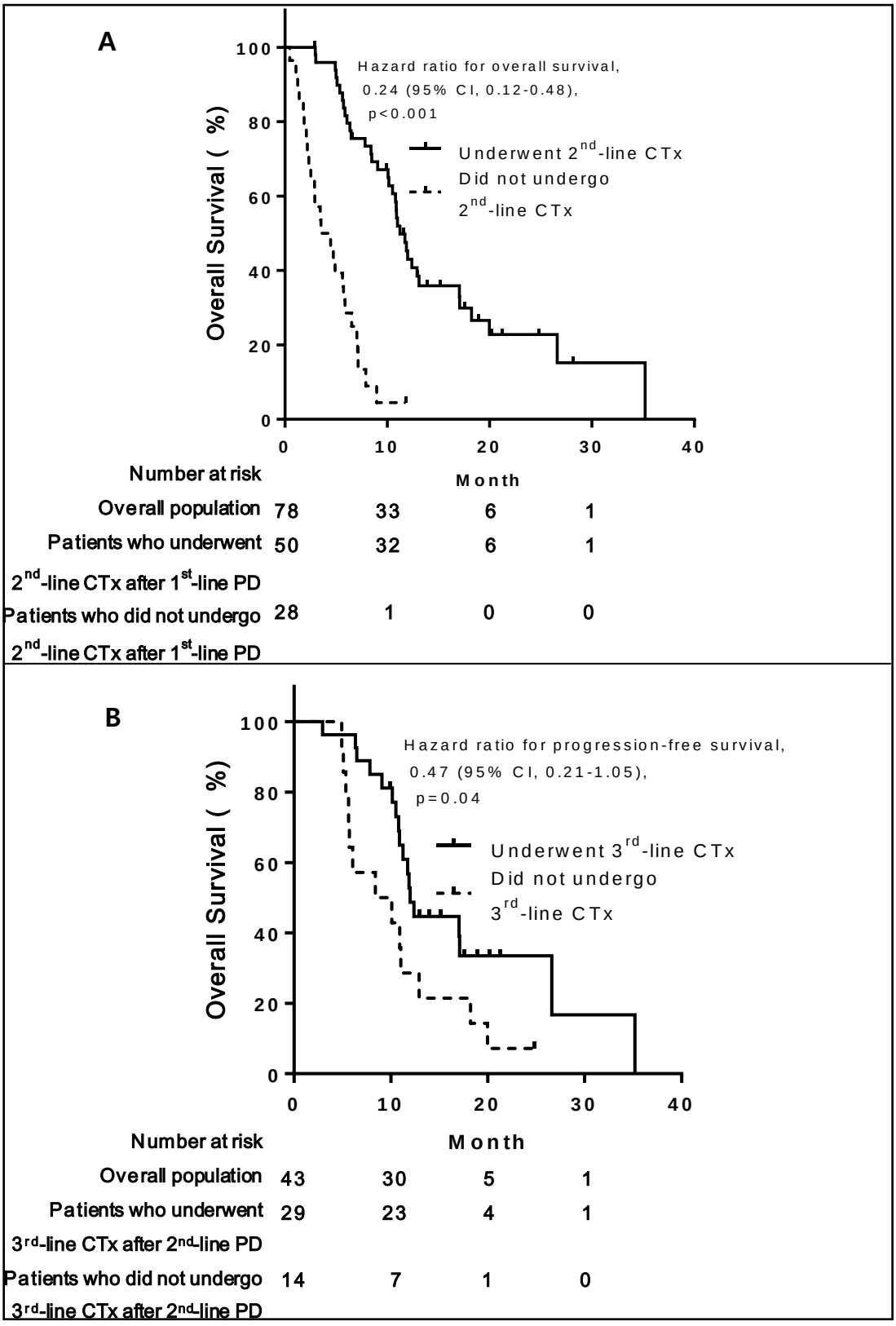
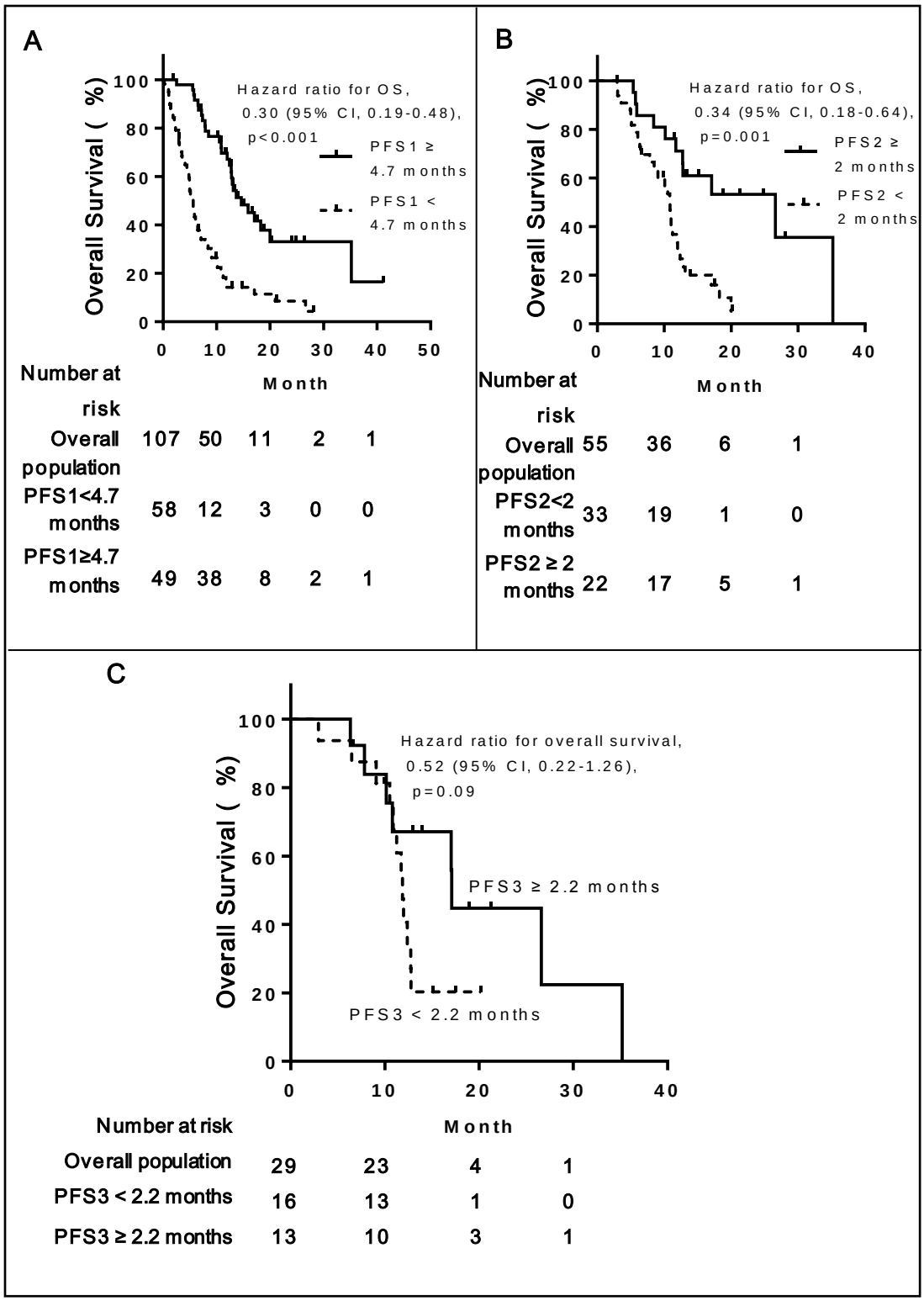


Figure 5. (A) Kaplan-Meier estimates of OS of palliative chemotherapy in esophageal squamous cell carcinoma, according to PFS after 1st-line chemotherapy.

(B) Kaplan-Meier estimates of OS of palliative chemotherapy in esophageal squamous cell carcinoma, according to PFS after 2nd-line chemotherapy.

(C) Kaplan-Meier estimates of OS of palliative chemotherapy in esophageal squamous cell carcinoma, according to PFS after 3rd-line chemotherapy



국문 요약

배경: 재발성/전이성 식도 편평상피세포암에서, 효과적이고, 견디기 쉬운 치료옵션은 제한되어 있다. 항암치료 차수에 따른 고식적 항암치료의 효과에 대한 자료 또한 제한적이다. 본 연구에서는 항암치료 차수에 따른 무진행 생존기간을 후향적으로 분석하였다.

대상 및 방법: 2015 년 3 월부터 2017 년 10 월까지 재발성/전이성 식도 편평상피세포암에 대하여 아산병원에서 고식적 항암치료를 시작한 모든 107 명의 환자들이 연구에 포함되었고, 이전에 시행된 완치목적의 치료에 따라 분류되었다; 그룹 A (이전 항암방사선치료 단독, 30 명), B (이전 수술적 치료 단독, 11 명), C (이전 항암방사선 및 수술적 치료, 30 명), D (이전 치료력 없음, 36 명). 그룹 A, B, C (71=30+11+30 명, 이전 치료그룹) 그리고 그룹 D (36 명, 이전 치료력 없는 그룹)는 이전 치료여부에 따라 재분류되었다. 전체 반응률, 생존률 자료는 각각의 그룹과 항암치료 차수, 항암제 종류에 따라 분석되었다.

결과: 이전 치료그룹과 이전 치료력 없는 그룹의 기본적 특성에는 큰 차이가 없었다 (원격전이여부 및 TNM stage 제외). 전체 반응률은 1, 2, 3 차 항암치료에서 각각 25.2%, 7.3%, 3.4% 였다. 중간 무진행 생존기간은 1, 2, 3 차 항암치료에서 각각 4.7, 2.0, 2.2 개월이었다. 전체 생존기간의 중간값은 이전 치료그룹과 이전 치료력 없는 그룹 사이에 유의한 차이가 없었다 (p=0.88). 다변량분석에 따르면 이전 수술적 치료 시행, 좋은 전신활동도, 3 차 이상의 항암치료 시행, 낮은 C-reactive protein 수치가 긴 전체생존기간과 유의하게 연관이 있었다.

결론: 무진행 생존기간은 고식적 항암치료의 차수가 진행함에 따라 빠르게 감소하였다. 전체 생존기간의 중간값은 이전 치료그룹과 이전 치료력 없는 그룹 사이에 유의한 차이가 없었다. 환자가 견딜 수 있다면, 추가적인 차수의 항암치료를 진행하는 것이 환자의 생존에 도움이 될 수 있다.