# Factors Affecting Survival in Operated Esophageal Squamous Cell Carcinoma

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# Abstract

**Purpose:** Esophageal squamous cell carcinoma (ESCC) is an extremely fatal and relatively rare gastrointestinal system malignancy. This study aimed to investigate the factors affecting survival in operated patients with ESCC.

**Materials and Methods:** We included 110 patients (38 [34.5%] male; 72 [65.5%] female) aged ≥18 (median age, 54 [26–77]) years who were operated without any signs of metastases and followed up at Van Yüzüncü Yıl University Dursun Odabaşı Medical Center between 2004 and 2019.

**Results:** Initially, 39 (35.5%) patients were clinical lymph node-positive and 71 (64.5%) patients were negative. Thirty-five (31.8%) patients underwent surgery after neoadjuvant chemoradiotherapy (nCRT) and 75 (%68.2) patients underwent direct surgery without nCRT. Five-year overall survival (OS) was 84.4% and 59.2% in patients who underwent surgery after nCRT and in those who underwent direct surgery, respectively. Median OS was significantly longer in patients who underwent surgery after nCRT (p=0.003). There was a statistically significant difference in OS in patients who underwent surgery after nCRT depending on tumor response (p=0.04). In multivariate analysis, advanced pathologic stage (p=0.002) adversely affected survival, whereas nCRT administration (p=0.031) positively affected OS.

**Conclusion:** We suggest that nCRT should be administrated before surgery, especially in locally advanced ESCCs. In addition, we believe that nCRT response can be used as a good parameter for survival. These results, however, should be supported by prospective studies.


# Introduction

Esophageal cancer is an extremely lethal malignancy, which accounts for approximately 17,750 cases of esophageal cancer diagnosed and 16,080 deaths annually in the US alone [1]. Esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC) account for >95 % of esophageal cancers. Furthermore, in the US, while the incidence of ESCC has decreased, the number of EAC cases has considerably increased in the last few years. However, ESCC remains the most prevalent histological subtype worldwide [2-4].

In previous studies, some risk factors associated with ESSC have been identified. It is estimated that 90% of ESCC cases in the US may have resulted from tobacco smoking, excessive alcohol consumption, and low vegetable and fruit intake. The distribution of these risk factors, however, showed significant differences in the rest of the world. For instance, in Asian countries, although the main risk factors remain unclear, several factors including malnutrition, low vegetable and fruit intake, and hot beverage consumption may have played a role in the pathogenesis [5-9].

Regardless of the histological subtype, approximately 50%–80% of ESCC cases are diagnosed at locally advanced or metastatic stages of the disease [6]. In the earliest stages, surgery is the recommended treatment option, whereas neoadjuvant chemoradiotherapy (nCRT), followed by surgery, is the standard

of care in locally advanced stages. However, the 5-year overall survival (OS) rate for patients with locally advanced stage rarely exceeds 30% [10, 11].

Previous studies have reported that the stage, Glasgow prognostic score, neutrophil-to-lymphocyte ratio, plasma squamous cell carcinoma antigen, and cytokeratin 19 were significant prognostic markers [12-16]. In this retrospective study, we aimed to analyze the factors affecting survival in operated patients with ESCC.

# Materials And Methods

*Study population*

In this retrospective study, we included patients with ESCC who were treated and followed up at the Department of Medical Oncology, Van Yüzüncü Yıl University between 2004 and 2019. Patients who were operated due to ESCC, non-metastatic patients, aged ≥18 years, with middle and lower localized tumor, and those without missing data were enrolled in the study. The exclusion criteria of the study were: histological subtypes other than ESCC, proximally located tumor, age <18 years, unoperated patients, second primary cancer, and those with missing data. Overall, 110 eligible patients were included in the final analysis.

*Variables and follow up*

The baseline characteristics of the patients included gender, age, comorbidities (diabetes mellitus [DM], hypertension [HT], chronic obstructive pulmonary disease [COPD], and chronic ischemic heart disease [CIHD]), initial symptom (obstruction, dysphagia, abdominal pain, and weight loss), Eastern Cooperative Oncology Group (ECOG) Performance Status (PS), primary tumor localization, grade, clinical stage, nCRT (yes vs. no), the regimens used for nCRT (carboplatin + paclitaxel or cisplatin + 5-fluorouracil), response to nCRT, pathological stage, adjuvant treatment (yes vs. no) and the regimens used in the adjuvant setting (5- fluorouracil + calcium folinate, carboplatin-paclitaxel, or cisplatin + 5-fluorouracil), recurrence (yes vs. no), site of recurrence, and last status (dead or alive) were obtained from hospital medical records. The clinical stages before the surgery were performed utilizing the initial whole-body computed tomography or 18 F-fluorodeoxyglucose positron emission tomography. The patients were grouped into 2 according to the ECOG PS as 0–1 (Asymptomatic–Symptomatic but completely ambulatory) or 2–3 (Symptomatic, <50% in bed during the day–Symptomatic, >50% in bed, but not bedbound). The tumor localization was categorized as middle (1/3) and lower (1/3). Patients who have been operated after nCRT were grouped according to the treatment response: complete response (pCR) fibrosis with no evidence of tumor cells, partial response (PR) fibrosis with rare residual tumor cells, and stable disease (SD) is fibrosis and gross residual tumor. OS was estimated as the time from the date of diagnosis to the date of death or last control.

*Treatments*

During nCRT and adjuvant chemotherapy, RT (radiation therapy) was delivered at 1.8 Gy daily fractions to a total dose of 41.4–50.4 Gy. The chemotherapy regimens used with RT were: carboplatin (AUC [area under the curve] 2, IV on day 1, weekly for 5 weeks) + paclitaxel (50 mg/kg, IV on day 1, weekly for 5 weeks) or cisplatin (75–100 mg/kg, IV, on day 1 and 29) + 5-fluorouracil (1000 mg/kg, IV continuous infusion over 24 h on day 1–4 and 29–33). In the adjuvant setting, carboplatin (AUC2, IV on day 1, weekly for 5 weeks) + paclitaxel (50 mg/kg, IV on day 1, weekly for 5 weeks) or cisplatin (75–100 mg/kg, IV, on day 1 and 29) + 5-fluorouracil (1000 mg/kg, IV continuous infusion over 24 h on day 1–4 and 29–33).

*Statistical analysis*

Statistical Package for Social Sciences 22.0 for Windows software (Armonk NY, IBM Corp. 2013) was used for the statistical analysis. Descriptive statistics were presented as standard deviation, minimum, maximum, and mean for numerical variables and percentage or number for categorical variables. Numerical variables between two independent groups were analyzed using Student's t-test when the normal distribution condition was met; otherwise, the Mann–Whitney U test was used. The comparison of rates between groups was analyzed using the chi-square test. Survival analyzes were performed using Kaplan–Meier analysis. The determinant factors were analyzed using Cox regression analysis. The backward stepwise model was used for p-values >0.150 in univariate analysis. The statistical alpha significance level for p-values was accepted as <0.05.

*Ethical approval*

This study was performed according to the Declaration of Helsinki. The study was reviewed and approved by the ethical committee of Yüzüncü Yıl University, Faculty of Medicine (Approval number: 2019/18-13).

# Results

Overall, 110 patients (38 [34.5%] male, 72 [65.5%] female) aged ≥18 (median age, 54 [26–77]) years were included. There were 14 (12.7%) patients with HT, 4 (3.6%) patients with DM, 4 (3.6%) patients with CIHD, and 4 patients (3.6%) with COPD. The most common presenting symptoms at the time of diagnosis were: dysphagia (94.5%), weight loss (22.2%), and abdominal pain (13.9%) (Table I).

The pathological stage was I in 30 (27.3%) patients, II in 45 (40.9%) patients, and III in 35 (31.8%) patients. Approximately 35 (31.8%) patients received nCRT before surgery. The rates of CR, PR, and SD after nCRT were 15 (42.9%), 13 (37.1%), and 7 (20%), respectively. During the follow-up period, recurrence occurred in 36 (32.7%) patients, 36 (32.7%) of whom died. The sites of recurrence in decreasing order of incidence were: liver (36.1%), distant lymph node (27.8%), locoregional (27.8%), and lung (8.3%) (Table I).

According to the pathological stages (I, II, and III) and nCRT status (yes vs. no), the 1- 2-, 3-, 5-, and 10-year OS rates are shown in Table II. The OS rates were significantly different among the pathological stages, with patients in stage III disease having the worst OS (35 months vs. not reached vs. not reached) (Fig. 1).

In Kaplan–Meier analysis, the OS of patients who received nCRT was significantly longer than those who did not receive neoadjuvant therapy (Log rank=0.03) (Fig. 2A). Considering survival based on the nCRT response, there were significant differences in OS among the response groups, with the best OS rates observed in patients with CR (Log rank=0.04) (Fig. 2B).

Univariate analysis showed that the presence of obstruction, ECOG PS, nCRT, clinical and pathological stage, and adjuvant treatment were the factors affecting OS (p=0.007, p=0.001, p=0.003, p=0.018, p=0.001, and p=0.036, respectively). In the multivariate analysis created with p-value <0.05 parameters with the entered model, nCRT and pathological stage were found to be the factors associated with OS in multivariate analysis (p= 0.031 and p= 0.002, respectively) (Table III).

# Discussion

In this retrospective study, we investigated the factors affecting survival in operated patients with ESCC. We observed better survival in patients treated with nCRT and worse survival duration as the pathological stage increased.

In ESCC, esophageal obstruction due to tumor causes progressive dysphagia, often accompanied by weight loss. Dysphagia generally occurs when the esophageal lumen diameter is <13 mm, indicating advanced disease [17]. In this study, dysphagia and obstruction were observed in 95% and 16.4% of the patients, respectively. In ESCC, although the main risk factors remain unclear, malnutrition, low vegetable and fruit intake, and hot beverage consumption are believed may play a role in the pathogenesis [5].

There is no obvious gender difference in regions where ESCC is endemic. However, it is more prevalent in men in low-incidence countries [18]. In this study, the female-to-male ratio was almost two-folds because it was conducted in a high-incidence region for ESCC. Low vegetable and fruit intake and some traditional nutritional habits in our region were quite common, such as salty cheese and hot tea consumption. Furthermore, of the patients included here, 30% were active smokers. A review from our country that included 31 studies between 1988 and 2010 suggested that the frequency of smoking ranged from 27.5% to 63.8% in males and 8.4%–27.8% in females [19]. In this study, the lower rate of smoking resulted from the high female-to-male ratio.

A study conducted by Javle et al. that included 172 patients with esophageal cancer, 74 of whom were ESCC, reported that tumor stage and surgery independently affected survival [20]. Suzuki et al. conducted a study on patients with ESCC and reported that stage independently affected survival [21]. Similarly, in this study, a higher stage significantly decreased survival and mortality rate in pathological stage III patients was nearly 5-folds higher than those in stage I.

In RTOG 85-01 study, Al Sarraf et al. compared RT to definitive nCRT in 123 locally advanced patients with esophageal cancer. mOS was 14.1 months in nCRT arm vs. 9.3 months in RT arm. Furthermore, another 69 patients were treated with CRT and the OS rate was 17.2 months, similar to the previous outcomes [22]. In another study that randomized 172 locally advanced patients with esophageal cancer

to induction chemotherapy, followed by nCRT plus surgery or definitive CRT, no significant survival difference between the groups was observed during the median 6-years follow-up. The 2-year locoregional control rate was found to be better in the surgery arm [23]. In the meta-analyses of studies comparing nCRT vs. surgery alone, nCRT was found to be superior [24-26].

In the meta-analysis that included 14 randomized studies conducted by Jin et al., it was observed that local control rates and survival rates with nCRT were better than surgery alone [24]. Likewise, in the meta-analysis of 9 randomized studies conducted by Urschel et al., it was observed that both 3-year survival and local control rates were better in the nCRT arm than surgery alone [25]. A study conducted by Munch et al. including 95 patients with ESCC compared nCRT with surgery or definitive CRT and found that a higher rate of local tumor control was observed in patients treated with nCRT than in patients treated with definitive CRT. There was at least a trend towards an improved OS and PFS in patients undergoing nCRT [27]. In this study, 75 patients were operated without nCRT, while 35 patients were operated without nCRT. OS was significantly longer in patients operated after nCRT. The 5-year survival rate was 84.4% in those operated after nCRT and 59.5% in patients who underwent direct surgery. In addition, administration of nCRT before surgery decreased the mortality by 68.5%.

There are limited studies in the literature that investigated the effect of pathological response after nCRT on survival only in ESCC. The results of the histological subtypes (ESCC and EAC) of esophageal cancer were given together in previous studies. In the study conducted by Takeda et al., pCR after nCRT in esophageal cancer significantly improved survival. Of 134 patients included in the study, only 94 were ESCC [28]. Likewise, in the study conducted by Gua et al. including 122 patients, only 43 patients were ESCC and found that the degree of tumor regression correlated with survival. The authors argued that tumor regression grade can be used to predict the long-term survival of esophageal cancer patients [29]. In this study, however, survival was significantly prolonged as the tumor response improved. At a median follow-up of 35 months, no recurrence or death was observed in any patient with pCR.

Unlike other studies, this study only included patients with ESCC and presented real-life data. In addition, only operated patients were included to ensure homogeneity. However, this study was designed retrospectively and as a single center. Furthermore, this study was conducted in a region where esophageal cancer is endemic, thus we were unable to determine how this could affect the results of the study.

In conclusion, administration of nCRT and early clinical stage in patients with ESCC were found to be the most important factors affecting survival in this study. It was observed that survival was prolonged as the tumor response improved in those who were operated after nCRT. We suggest that nCRT should be administered before surgery, especially in locally advanced ESCC. In addition, we believe that nCRT response can be used as a good parameter for survival. These results should be supported by prospective clinical studies.

# Declarations

**Informed consent statement:** Patients were not required to given informed consent for the study, because analyzes were used retrospectively with anonymous clinical data obtained after each patient accepted treatment with written consent.

**Conflict-of-interest statement:** All authors declare no conflicts-of-interest.

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**Author Contributions:** Concept – NA, SS, AS; Design – NA, MNQ, AA; Supervision – MA, UHI, MCK; Resources – NA, SS, AA, UHI; Materials – AS, MNA, MA, MCK; Data Collection and/or Processing – NA, AS, SS; Analysis and/or Interpretation – AS, SS, AA, MNA; Literature Search – MA, UHI, MCK; Writing Manuscript – NA, AS, SS, MCK; Critical Review – AA, MA, UHI; Other – AS, MNA, AA, UHI.

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# Tables

**Table I.** Patients' Data

| Characteristics | | N | % |
|---|---|---|---|
| Gender | Men | 38 | 34.5 |
| | Women | 72 | 65.5 |
| Age (year) | Median (Min-Max) | 54 (26-77) | |
| Comorbidities | HT | 14 | 12.7 |
| | DM | 4 | 3.6 |
| | CIHD | 4 | 3.7 |
| | COPD | 5 | 4.6 |
| Smoking status | No | 80 | 72.7 |
| | Yes | 30 | 27.3 |
| Initial symptom | Obstruction | 18 | 16.4 |
| | Dysphagia | 104 | 95.4 |
| | Abdominal pain | 15 | 13.9 |
| | Weight loss | 24 | 22.2 |
| ECOG PS | 0 | 53 | 50.5 |
| | 1 | 46 | 43.8 |
| | 2 | 4 | 3.8 |
| | 3 | 2 | 1.9 |
| Primary tumor localization | 2/3 | 73 | 66.4 |
| | 3/3 | 37 | 33.6 |
| Grade | Good | 17 | 16.7 |
| | Moderate | 69 | 67.6 |
| | Poor | 16 | 15.7 |
| Clinical stage | Lymph node negative | 71 | 64.5 |
| | Lymph node positive | 39 | 35.5 |
| nCRT | Yes | 35 | 31.8 |
| | No | 75 | 68.2 |
| The regimens used for nCRT | Carboplatin + Paclitaxel | 28 | 80.0 |
| | Cisplatin + 5-Fluorouracil | 7 | 20.0 |

| | | | |
|---|---|---|---|
| **Response to nCRT** | **CR** | 15 | 42.9 |
| | **PR** | 13 | 37.1 |
| | **SD** | 7 | 20.0 |
| **Pathological stage** | **I** | 30 | 27.3 |
| | **II** | 45 | 40.9 |
| | **III** | 35 | 31.8 |
| **Adjuvant treatment** | **No** | 82 | 79.6 |
| | **Yes** | 21 | 20.4 |
| | **Cisplatin + 5-Fluorouracil** | 15 | 13.6 |
| | **Carboplatin + Paclitaxel** | 6 | 5.4 |
| **Recurrence** | **No** | 74 | 67.3 |
| | **Yes** | 36 | 32.7 |
| **Site of recurrence** | **Locoregional** | 10 | 27.8 |
| | **Lung** | 3 | 8.3 |
| | **Liver** | 13 | 36.1 |
| | **Distant Lymph Node** | 10 | 27.8 |
| **Last status** | **Dead** | 36 | 32.7 |
| | **Alive** | 74 | 67.3 |

**Abbreviations: CIHD**, Chronic İschemic Heart Disease; **CR**, Complete response; **COPD**, Chronic Obstructive Pulmonary Disease; **DM**, Diabetes mellitus; **ECOG PS**, Eastern Cooperative Oncology Group Performance Status; **HT**, Hypertension; **nCRT,** Neoadjuvant chemoradiotherapy; **PR**, Partial response, **SD**, Stabil disease.

**Table II.** Survival rates by years.

| Year | All patients | nCRT (+) | nCRT (-) | Stage I | Stage II | Stage III |
|---|---|---|---|---|---|---|
| **1** | 88.9 | 96.6 | 89.3 | 93.2 | 91.1 | 82.9 |
| **2** | 78.2 | 93.1 | 72.8 | 93.2 | 80.3 | 68.6 |
| **3** | 68.7 | 89.1 | 67.9 | 81.5 | 80.3 | 50.7 |
| **5** | 64.1 | 84.4 | 59.2 | 81.5 | 77.0 | 40.0 |
| **10** | 57.6 | 84.4 | 45.4 | 81.5 | 72.5 | 32.3 |

**Table III.** Univariate analysis and multivariate analysis for OS.

| Characteristics | | Univariate analysis for OS | | | Multivariate analysis for OS | | |
|---|---|---|---|---|---|---|---|
| | | HR | 95.0% CI For HR | P | HR | 95.0% CI For HR | P |
| Gender | Women vs. Men | 0.634 | | 0.179 | | | |
| Age | Year | 1.013 | 0.985-1.233 | 0.370 | | | |
| HT | Yes vs. No | 0.371 | 0.089-1.547 | 0.174 | | | |
| DM | Yes vs. No | 0.630 | 0.086-4.600 | 0.649 | | | |
| CIHD | Yes vs. No | 0.517 | 0.071-3.783 | 0.516 | | | |
| COPD | Yes vs. No | 1.009 | 0.242-4.208 | 0.990 | | | |
| Smoking | Yes vs. No | 0.761 | 0.346-1.669 | 0.495 | | | |
| Dysphagia | Yes vs. No | 1.228 | 0.167-9.013 | 0.840 | | | |
| Abdominal pain | Yes vs. No | 0.517 | 0.158-1.690 | 0.275 | | | |
| Weight loss | Yes vs. No | 0.890 | 0.388-2.038 | 0.782 | | | |
| Obstruction | Yes vs. No | 2.672 | 1.307-5.463 | ***0.007*** | | | |
| ECOG PS | 2-3 Vs 0-1 | 5.318 | 1.995-14.177 | ***0.001*** | | | |
| Primary tumor localization | 2/3 vs 3/3 | 1.055 | 0.249-4.461 | 0.942 | | | |
| Grade | Good (Ref.) | 1 | | 0.510 | | | |
| | Moderate | 1.859 | 0.642-5.381 | 0.253 | | | |
| | Poor | 1.875 | 0.502-7.001 | 0.350 | | | |
| nCRT | Yes vs. No | 0.211 | 0.074-0.596 | ***0.003*** | 0.315 | 0.110-0.902 | 0.031 |
| Clinical stage | Lymph node positive vs. | 2.207 | 1.147-4.245 | ***0.018*** | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Lymph node negative** | | | | | | |
| **Pathological stage** | **I (Ref.)** | 1 | | ***0.001*** | 1 | | 0.002 |
| | **II** | 1.391 | 0.435-4.448 | ***0.578*** | 1.554 | 0.425-5.676 | 0.505 |
| | **III** | 4.348 | 1.494-12.653 | ***0.007*** | 4.883 | 1.441-16.540 | 0.011 |
| **Adjuvant treatment** | **Yes vs. No** | 2.128 | 1.049-4.315 | ***0.036*** | | | |
| | | | | | | | |

**Abbreviations:** see *table 1*.

# Figures

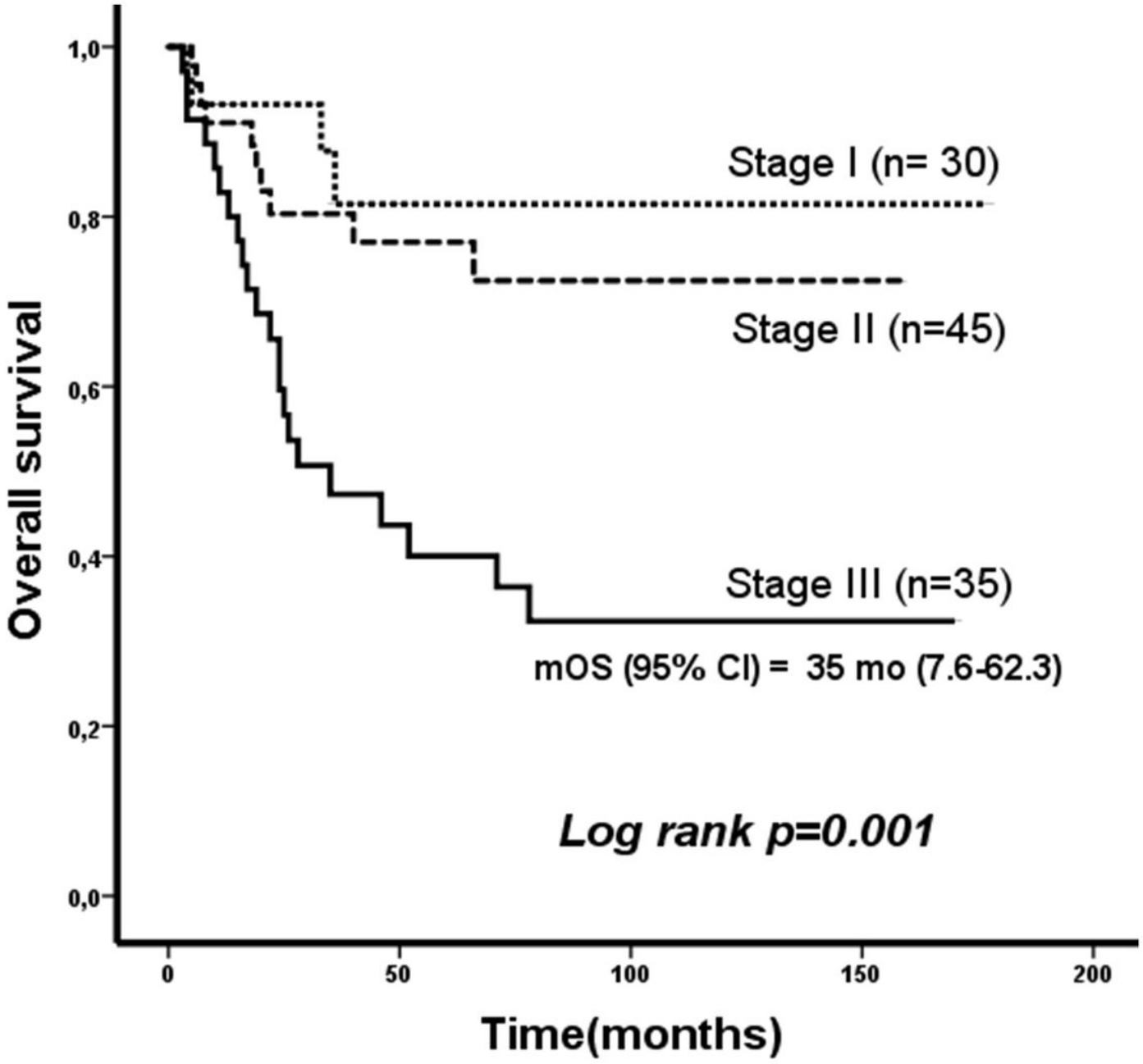
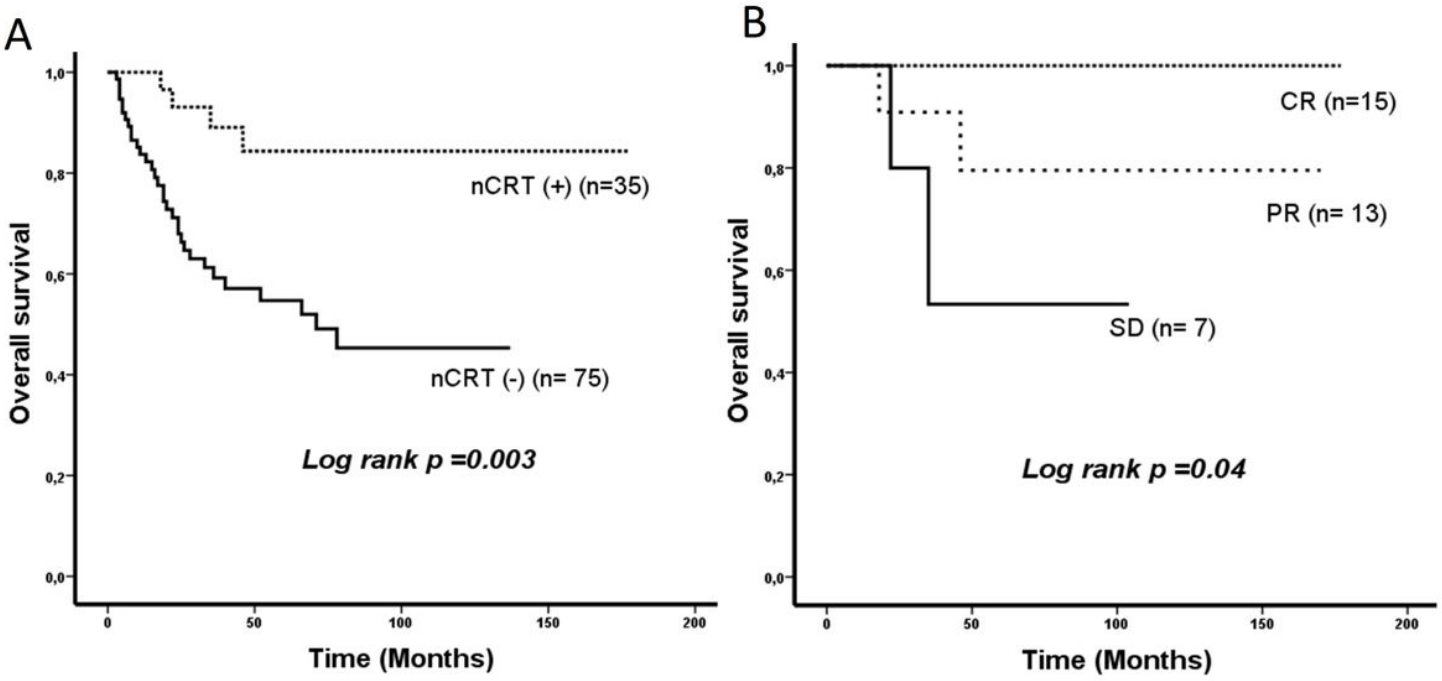



**Figure 1**

Overall survival according to pathologic tumor stage.




## Figure 2

Overall survival according to nCRT status (A) and nCRT response (B).