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Survival Impact of Adjuvant Chemoradiotherapy in Resected Pancreatic Cancer

Opere Pankreas Kanserinde Adjuvan Kemoradyoterapinin Sağkalım Etkisi

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ABSTRACT

Aim: Pancreatic cancer (PC) is one of the most aggressive cancers, with a 5-year survival rate of less than 50% in resectable stages. The aim of this study was to determine the survival effect of adjuvant chemoradiotherapy (CRT) in resected PC.

Materials and Methods: We retrospectively analyzed 156 patients with resected PC, who received adjuvant chemotherapy with/without CRT. The Cox regression and Kaplan-Meier analyses were used to determine the factors related to survival rate. Subgroup analyses were performed according to clinical characteristics.

Results: The number of patients with lymph node metastases was statistically significantly higher in patients receiving CRT (p=0.007). No effect of CRT on both disease-free survival (DFS) and overall survival was detected (p>0.05). Subgroup analysis of DFS showed that adjuvant CRT was associated with poor prognosis in patients with in patients with in patients with low Eastern Collaborative Oncology Group performance scores (p=0.043), low T-stage (p=0.024), or low De-Ritis ratio (p=0.030). Subgroup analysis indicated that the overall survival benefit of adjuvant CRT was more significant in patients without diabetes mellitus (p=0.040), low serum carbohydrate antigen 19-9 levels (p=0.047), or low hemoglobin values (p=0.046).

Conclusion: Our study has shown that the survival benefits of adding CRT to adjuvant chemotherapy in operated PC patients are limited. Patients who will receive CRT must be carefully selected according to their clinicopathological characteristics.

Keywords: Pancreatic cancer, adjuvant therapy, chemoradiotherapy, radiotherapy, survival

ÖZ

Amaç: Pankreas kanseri (PK), rezeke edilebilir evrelerde 5 yıllık sağkalım oranı %50'den az olan en agresif kanserlerden biridir. Bu çalışmanın amacı rezeke edilmiş PK'de adjuvan kemoradyoterapinin (CRT) sağkalım etkisini belirlemektir.

Gereç ve Yöntem: Opere edilmiş PK'li ve adjuvan kemoterapi alan 156 hastayı retrospektif olarak analiz ettik. Sağkalım oranıyla ilişkili faktörleri belirlemek için Cox regresyon ve Kaplan-Meier analizleri kullanıldı. Alt grup analizleri klinik özelliklere göre yapıldı.

Bulgular: Lenf nodu metastazı olan hasta sayısı, CRT alan hastalarda istatistiksel olarak anlamlı derecede daha yüksekti (p=0,007). CRT'nin hem hastalıksız sağkalım (DFS) hem de genel sağkalım üzerinde bir etkisi saptanmadı (p>0,05). DFS'nin alt grup analizi, adjuvan CRT'nin düşük Doğu İşbirliği Onkoloji Grubu performans skorları (p=0,043) veya düşük T-evresi (p=0,024) veya düşük De-ritis oranı (p=0,030) olan hastalarda kötü prognozla ilişkili olduğunu gösterdi. Alt grup analizi, adjuvan CRT'nin genel sağkalım faydasının non-diabetes mellitus (p=0,040) veya düşük serum

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karbohidrat antijeni 19-9 seviyeleri (p=0,047) veya düşük hemoglobin değerleri (p=0,046) olan hastalarda daha anlamlı olduğunu gösterdi.

Sonuç: Çalışmamız, ameliyat edilen PK hastalarında adjuvan kemoterapiye CRT eklemenin sağkalım faydalarının sınırlı olduğunu gösterdi. CRT alacak hastalar klinikopatolojik özelliklerine göre dikkatlice seçilmelidir.

Anahtar Kelimeler: Pankreas kanseri, adjuvan tedavi, kemoradyoterapi, radyoterapi, sağkalım

INTRODUCTION

Pancreatic cancer (PC) is the twelfth most common cancer in the world and one of the leading causes of cancer deaths. PC exhibits a lethal disease course and is expected to become the second most common cause of cancer-related deaths in the next decades despite improved treatment strategies[1,2]. While its overall survival (OS) is 2.6%, it is responsible for 4.7% of cancer-related deaths, and the expected 5-year OS in the advanced stage is 3%[3]. In the operable stages, that is to have been potentially curable, the 5-year survival is less than 50%, even if they have received all planned treatments[2].

Surgery, chemotherapy, and radiotherapy (RT) (with/without chemotherapy) are substantial treatment options in the early or locally advanced stages of PC. The benefit of adjuvant chemotherapy after surgery in localized patients is clear and there is no controversy in this setting on guidelines[4-6]. Contrary to strong recommendations for chemotherapy, the importance of RT is unclear. In the light of studies and guidelines in the literature, RT is either included as a poor recommendation next to chemotherapy or is not recommended[4,7,8]. In addition, it is unclear whether RT provides a survival benefit or is a poor prognostic factor for survival.

In this study, we investigated the effect of adjuvant chemoradiotherapy (CRT) on survival by performing a comprehensive prognostic factor analysis in operated PC patients receiving adjuvant chemotherapy. In this way, we aimed to identify the patient populations that could benefit from adjuvant RT and to determine the most appropriate prognostic factors to guide cancer treatment professionals in clinical practice.

MATERIALS AND METHODS

Study Population

This study was planned as a multicenter-retrospective study and conducted in accordance with the Declaration of Helsinki. Approval from the Non-Interventional Clinical Research Ethics Committee of Tekirdağ Namık Kemal University (TNKU) Faculty of Medicine (decision no: 2022.159.09.06, date: 27.09.2022). Data were collected from participating medical oncology clinics. Patients aged >18 years who underwent surgery for PC and received adjuvant chemotherapy between March 2016 and June 2022 were included. Patients with metastatic disease, concomitant or previous malignancy, positive margins, having received neoadjuvant therapy, or patients who did not complete the planned adjuvant chemotherapy were excluded from the study.

All patients who received RT were given treatment as CRT (with capecitabine/5-fluorouracil). As a RT protocol in the included centers, patients generally receive RT (3-dimensional conformal RT or intensity-modulated RT) for 5 days a week (28 fractions) for approximately 5.5 weeks within 7-21 days after the completion of chemotherapy. During RT, patients receive either capecitabine twice a day for 5 days a week or 5-fluorouracil continuously for 5.5 weeks or until RT is completed.

Data Collection

Three centers with oncology expertise were included in the study. Patients' demographics, clinicopathologic data, and serum laboratory parameters measured prior to initial chemotherapy were documented. Prognostic nutritional index (PNI), neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and De Ritis (aspartate transaminase-to-alanine transaminase ratio) were measured and recorded from laboratory data. The calculation formula for the globulin was total protein-serum albumin, and that for PNI was 10 × serum albumin (g/dL) + 0.005 × lymphocyte count (per mm^3).

Statistical Analysis

Statistical analyses were performed using SPSS Statistic software 24 (SPSS Inc., Chicago, III). The ROC curve and area under the curve were used as optimal cut-off values for laboratory parameters and indices, but the optimal cut-off could not be determined. Therefore, median values were accepted as cut-off values. For the analysis of categorical variables, the chi-square test or Fisher's exact test were utilized. These cut-offs were used to differentiate the two groups as "low" and "high." Firstly, univariate and multivariate analyses of factors affecting OS and Progression-free Survival were performed with Cox Proportional Hazards Model. Secondly, two separate groups were formed with and without CRT, and potential prognostic factors were investigated by subgroup analysis using univariate Cox analysis. Hazard ratio (HR) was reported with the corresponding 95% confidence intervals (CI)

(95% CI). Thirdly, the factors that were found to be statistically significant in the subgroup analysis were compared with the Kaplan Meier and Log-Rank tests. The OS was calculated as the time from randomization to all-cause death or the last follow-up date used for censoring. Disease-free survival (DFS) was considered as time to relapse or all-cause death, whichever came first. Statistical significance was accepted as $p<0.05$.

RESULTS

Patient Characteristics

A total of 1128 patients were examined. Eight hundred forty-nine patients were found to be in the metastatic stage, and 123 patients had no laboratory data before the first treatment. These patients were excluded, and the study was completed with 156 patients. The median age was 62 years (range: 35-82 years). One hundred (64.1%) of the patients were male. Of all study patients, 114 (73.1%) relapsed and 104 (66.7%) died of cancer-related causes. The median follow-up time among all studies was 73.0 months (range: 63.7-82.3). The median DFS was 20.6 months (95% CI: 16.6-24.6) in all patients, 17 months (95% CI: 13.2-20.9) in those receiving adjuvant CRT and 23.3 months (95% CI: 18.9-27.7) in those not receiving CRT. The median OS was 80 months (95% CI: 70.5-89.5) in all patients, 101.3 months (95% CI: 56.4-146.2) in those receiving CRT and 77.5 months (95% CI: 65.3-89.7) in those not receiving CRT.

Demographic and clinicopathologic characteristics of patients who received CRT and those who did not receive RT were similar. The number of patients with lymph node metastases was statistically significantly higher in patients who received only CRT (p= 0.007). The general characteristics and laboratory data of the patients, compared according to the CRT groups, are shown in Table 1.

Survival Analysis

For survival analysis, the median values of 2.92 for carcinoembryonic antigen, 39.94 for carbohydrate antigen 19-9 (CA 19-9) 12.1 for hemoglobin, 0.75 for total bilirubin, 2.63 for NLR, 155.12 for PLR, 1.09 for De-Ritis, and 48.9 for PNI were accepted as cut-off. In the Cox regression analysis, low body mass index (HR=1.50, 95% CI: 1.0-2.23, p=0.047), higher T-stage (HR=1.55, 95% CI: 1.06-2.27, p=0. 026), lymph node metastasis (HR=1.67, 95% CI: 1.13-2.47, p=0.010) and higher De-ritis (HR=1.50, 95% CI: 1.03-2.17, p=0.032) were associated with lower DFS. Diabetes mellitus (DM) (HR=2.24, 95% CI: 1.22-4.12, p=0.009), tumor localization outside the pancreatic head (HR=1.91, 95% CI: 1.08-3.37, p=0.026) and high CA 19-9 level (HR=1.99, 95% CI: 1.09-3.64, p=0.025) were found to be poorly prognostic for OS. Adjuvant CRT had No survival effect for both DFS and OS (p=0.490, p=0.090, respectively) (Table 2). In established multivariate models, lymph node status (HR=1.67, 95% CI: 1.13-2.47, p=0.010) for DFS and DM (HR=3.06, 95% CI: 1.61-5.81, p=0.001) and tumor localization (HR=2.37, 95% CI: 1.31-4.30, p=0.004) for OS were found to be independent prognostic factors.

Association of Adjuvant CRT with Survival, Subgroup Analysis

Subgroup analyses were performed to identify groups that could benefit or suffer from CRT. No subgroup that adjuvant CRT contributed positively to DFS was found. Adjuvant CRT was associated with worse survival in good ECOG performance status (HR=1.65, 95% CI: 1.02-2.69, p=0.043), low pathologic T (pT) (HR=2.05, 95% CI: 1.10-3.82, p=0.024) and low De-ritis ratio (HR=1.85, 95% CI: 1.06-3.24, p=0.030) (Table 3). Survival curves were made by the Kaplan-Meier analysis. The corresponding mDFS values according to ECOG performance scores and pT stage were 17.0 (95% CI: 12.3-21.8) versus 29.2 months (95% CI: 18.0-40.5) (log rank p=0.040), 17.0 months (95% CI: 7.7-26.3) versus 52.8 months (95% CI: 23.4-82.2) (log rank p=0.021), and 16.8 (95% CI: 12.4-21.2) versus 23.5 months (95% CI: 16.2-30.8) (log rank p=0.046), respectively, with significant difference (Figure 1).

The Cox regression analysis found that adjuvant CRT also did not provide survival for OS. In subgroup analysis, CRT provided longer OS in those with non-DM (HR=0.46, 95% CI: 0.22-0.97, p=0.040), low CA 19-9 levels before treatment (HR=0.42, 95% CI: 0.18-0.99, p=0.047) and low hemoglobin values (HR=0.35, 95% CI: 0.13-0.98, p=0.046) (Table 3). Survival curves were made by the Kaplan-Meier analysis. The corresponding mOS values according to without-DM, low CA 19-9, and low hemoglobin values were 139 (95% CI: 48.4-229.7) versus 80 months (95% CI: 75.6-84.5) (log rank p=0.045), 139 months (95% CI: 97.9-180.2) versus 80.1 months (95% CI: 66.4-94.8) (log rank p=0.042), and 101.3 (95% CI: 58.3-144.3) versus 69.9 months (95% CI: 54.8-85) (log rank p=0.037), respectively, with significant difference (Figure 1).

DISCUSSION

In this study, we addressed the relationship between adjuvant CRT and survival in PC patients who underwent surgery and received adjuvant chemotherapy. Our study found that adjuvant CRT had no impact on both DFS and OS. In subgroup analyses, CRT was associated with worse survival times with good ECOG performance, low pT stage and low De-ritis rate. CRT was associated with longer OS times in without-DM, low CA 19-9 values and low hemoglobin values. Significant survival benefits have been achieved in operable PC with adjuvant chemotherapy[9,10]. However, chemotherapy alone does

not provide the desired contribution to survival, indicating the need for new treatment methods. Among the studies on adjuvant CRT, although the Gastrointestinal Tumor Study Group study conducted in 1974 was superior to RT alone, the EORTC-3 study with a similar design revealed that CRT was not superior to the observation arm[11,12]. A large patient analysis conducted by 2013 reported that chemotherapy followed by CRT was not favorable in prolonging survival.

Table 1. Demographic and clinicopathological features of patients regarding chemoradiotherapy and chemotherapy alone

	Total	Non-CRT	CRT	
	n (%)	n (%)	n (%)	p-value
Clinicopathological characteristics	156 (100)	101 (64.7)	55 (35.3)	
Age (year)				
<65	96 (61.5)	60 (62.5)	36 (37.5)	0.458
≥65	60 (38.5)	41 (68.3)	19 (31.7)	
ECOG-PS				
<2	95 (60.9)	56 (58.9)	39 (41.1)	0.059
≥2	61 (29.1)	45 (73.8)	16 (26.2)	
BMI				
<25	110 (70.5)	69 (62.7)	41 (37.3)	0.415
≥25	46 (29.5)	32 (69.6)	14 (30.4)	
Sex				
Male	101 (64.7)	69 (38.3)	32 (31.7)	0.206
Female	55 (35.3)	32 (58.2)	23 (41.8)	
Smoking history				
Yes	97 (62.2)	58 (59.8)	39 (40.2)	0.097
No	59 (37.8)	43 (72.9)	16 (27.1)	
Alcohol history				
Yes	30 (19.2)	23 (76.7)	7 (23.3)	0.128
No	126 (80.8)	78 (61.9)	48 (38.1)	
DM history				
Yes	53 (34)	36 (67.9)	17 (32.1)	0.551
No	103 (66)	65 (63.1)	38 (36.9)	
Primary site				
Head	102 (65.4)	63 (61.8)	39 (38.2)	0.284
Other	54 (34.5)	38 (70.4)	16 (29.6)	
pT				
<3	64 (41)	43 (67.2)	21 (32.8)	0.594
≥3	92 (59)	58 (63)	34 (37)	
Lymph node status				
Negative	59 (37.8)	46 (78)	13 (22)	**0.007**
Positive	97 (62.2)	55 (56.7)	42 (43.3)	
Histologic type				
Ductal adeno	143 (91.7)	91 (63.6)	52 (36.4)	0.545
Others	13 (8.3)	10 (76.9)	3 (23.1)	
Histologic grade				
Grade 1-2	133 (85.3)	85 (63.6)	48 (36.4)	0.600
Grade 3	23 (14.7)	16 (69.6)	7 (30.4)	
Chemotherapy regimes				
Gemcitabine based	97 (62.2)	60 (61.9)	37 (38.1)	0.333
İrinotekanlı/irinotekansız oksaliplatin	59 (37.8)	41 (69.5)	18 (30.5)	

CRT: Chemoradiotherapy, ECOG-PS: Eastern Cooperative Oncology Group Performance Status, DM: Diabetes mellitus, pT: Pathologic T, BMI: Body mass index

Table 2. Univariate analyses of factors for disease-free survival and overall survival

		DFS		OS	
Clinicopathological Characteristics	**Category**	**HR (95% CI)**	**p**	**HR (95% CI)**	**p-value**
Age (year)	<65/≥65	1.14 (0.78-1.68)	0.497	1.15 (0.65-2.03)	0.635
Gender	Female/male	0.97 (0.66-1.41)	0.845	0.94 (0.53-1.68)	0.839
BMI	<25/≥25	1.50 (1.0-2.23)	0.047	1.71 (0.89-3.31)	0.110
ECOG	0-1/≥2	1.38 (0.95-2.01)	0.090	1.30 (0.72-2.35)	0.382
Smoking history	No/Yes	0.99 (0.68-1.45)	0.977	1.03 (0.58-1.84)	0.910
Alcohol history	No/Yes	1.07 (0.66-1.74)	0.778	1.36 (0.67-2.75)	0.393
DM history	No/Yes	1.07 (0.73-1.59)	0.724	2.24 (1.22-4.12)	**0.009**
Primary site	Head/Others	0.72 (0.48-1.07)	0.107	1.91 (1.08-3.37)	**0.026**
pT stage	<3/≥3	1.55 (1.06-2.27)	**0.026**	0.78 (0.45-1.36)	0.387
Lymph node status	Negative/Positive	1.67 (1.13-2.47)	**0.010**	1.69 (0.93-3.07)	0.085
Histologic type	Ductal Adeno/Others	0.78 (0.40-1.55)	0.479	1.11 (0.47-2.65)	0.810
Histologic grade	1/2-3	1.33 (0.83-2.14)	0.236	1.08 (0.55-2.14)	0.822
Chemotherapy regimes	Gemcitabine/Oxaliplatin	1.03 (0.69-1.55)	0.880	0.66 (0.36-1.21)	0.179
CRT	No/Yes	1.15 (0.78-1.68)	0.490	0.60 (0.33-1.08)	0.090
Laboratory parameters					
NLR	<2.63/≥2.63	0.90 (0.63-1.31)	0.592	0.76 (0.44-1.33)	0.343
PLR	<155.12/≥155.12	1.01 (0.70-1.46)	0.959	0.99 (0.57-1.72)	0.960
De-Ritis	<1.09/≥1.09	1.50 (1.03-2.17)	0.032	0.86 (0.48-1.55)	0.625
PNI	<48.9/≥48.9	1.36 (0.94-1.96)	0.106	1.04 (0.59-1.81)	0.901
CEA (ng/mL)	<2.92/≥2.92	1.26 (0.87-1.82)	0.223	1.00 (0.58-1.74)	0.991
CA 19-9 (U/mL)	<39.94/≥39.94	1.45 (0.94-2.25)	0.096	1.99 (1.09-3.64)	0.025
Hemoglobin (g/dL)	<12.10/≥12.10	1.29 (0.89-1.86)	0.183	0.77 (0.44-1.35)	0.360

DFS: Disease-free survival, OS: Overall survival, HR: Hazard ratio, CI: Confidence interval, ECOG-PS: Eastern Cooperative Oncology Group Performance Status, DM: Diabetes mellitus, pT: Pathologic T, CRT: Chemoradiotherapy, NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, PNI: Prognostic Nutritional Index, CEA: Carcinoembryonic antigen, CA 19-9: Carbohydrate antigen 19-9, BMI: Body mass index

Moreover, it was observed that the combination arm was more toxic than chemotherapy alone[13]. Consistently, in our study, CRT did not provide a survival benefit for either DFS or OS. In addition to studies with no survival benefit, there are also studies in the literature reporting the negative effect of RT on survival times[14,15]. The conflicting results in the literature regarding the impact of adjuvant CRT on survival have prevented the adoption of adjuvant CRT in the guidelines.

Although CRT has a modest impact on survival, it is important to identify high-risk patients for whom CRT may be effective and patient groups for whom it has an adverse effect. The study by Shi et al.[16] and the study by Opfermann et al.[17] reported a survival benefit of CRT in lymph node positive patients. In our study, lymph node positivity was significantly higher in patients who received CRT compared to those who did not. In line with the literature, this suggests that lymph node status is considered an important factor in the selection of CRT candidate patients in our institution. However, in our study, lymph node status was not associated with survival times for CRT. In subgroup analysis, lymph node involvement was not associated with CRT for survival. This may be related to the fact that, unlike previous studies, all patients in our study received chemotherapy. This difference may be due to the fact that the studies showing a positive effect of CRT were mostly conducted against observation. Consistent with our study, CRT did not show a positive effect in the study of Van Laethem et al.[18], which included patients receiving chemotherapy. In addition, the significant numerical difference between the CRT and non-CRT groups may have contributed to this result.

Given the doubts about the survival effects of CRT and the complications of RT, it is important to choose the right treatment candidates for CRT[19,20]. In our study, no survival benefit was demonstrated for CRT in most of the subgroups. Moreover, the results were detrimental for DFS in groups including performance status, stage and De-Ritis rate. To the best of our knowledge, our study is the first to report

Table 3. Survival effect of chemoradiotherapy among subgroups

	DFS		OS	
Clinicopathological characteristics	**HR (95% CI)**	**p**	**HR (95% CI)**	**p-value**
Age (year)				
<65	1.18 (0.73-1.90)	0.496	0.62 (0.29-1.31)	0.208
≥65	1.017 (0.52-1.97)	0.960	0.46 (0.15-1.43)	0.181
ECOG-PS				
<2	1.65 (1.02-2.69)	**0.043**	0.56 (0.27-1.17)	0.121
≥2	0.66 (0.33-1.32)	0.237	0.67 (0.22-1.98)	0.465
BMI				
<25	1.02 (0.64-1.63)	0.924	0.67 (0.35-1.31)	0.242
≥25	1.63 (0.79-3.34)	0.186	0.44 (0.10-2.01)	0.294
Sex				
Male	1.09 (0.66-1.78)	0.746	0.64 (0.30-1.35)	0.242
Female	1.35 (0.73-2.51)	0.343	0.43 (0.14-1.40)	0.161
Smoking history				
Yes	1.07 (0.66-1.73)	0.796	0.55 (0.18-1.68)	0.298
No	1.35 (0.70-2.58)	0.368	0.63 (0.30-1.34)	0.231
Alcohol history				
Yes	0.51 (0.15-1.77)	0.292	1.00 (0.25-4.02)	0.995
No	1.33 (0.88-2.01)	0.182	0.61 (0.31-1.19)	0.147
DM history				
Yes	1.12 (0.56-2.24)	0.751	1.14 (0.41-3.17)	0.804
No	1.15 (0.72-1.82)	0.566	0.46 (0.22-0.97)	**0.040**
Primary site				
Head	1.05 (0.67-1.66)	0.825	0.55 (0.24-1.26)	0.155
Other	1.57 (0.82-3.00)	0.175	0.84 (0.34-2.07)	0.709
pT				
<3	2.05 (1.10-3.82)	**0.024**	0.53 (0.20-1.43)	0.211
≥3	0.78 (0.48-1.28)	0.325	0.58 (0.25-1.35)	0.208
Lymph node status				
Negative	0.90 (0.42-1.91)	0.784	0.39 (0.11-1.40)	0.153
Positive	1.09 (0.69-1.73)	0.708	0.56 (0.26-1.20)	0.137
Histologic type				
Ductal adeno	1.30 (0.87-1.92)	0.200	0.71 (0.38-1.34)	0.294
Others	0.14 (0.02-1.18)	0.071	0.02 (0.00-100.30)	0.371
Histologic grade				
Grade 1	1.21 (0.48-3.01)	0.685	0.16 (0.02-1.31)	0.087
Grade 2-3	1.12 (0.74-1.72)	0.590	0.72 (0.37-1.38)	0.717
Chemotherapy regimes				
Gemcitabine based	1.07 (0.69-1.66)	0.753	0.50 (0.25-1.00)	0.051
Oxaliplatin with/without irinotecan	1.78 (0.71-4.93)	0.205	2.82 (0.71-11.16)	0.141
NLR				
<2.63	0.81 (0.46-1.42)	0.454	0.88 (0.40-1.90)	0.737
≥2.63	1.57 (0.92-2.67)	0.100	0.40 (0.15-1.09)	0.072
PLR				
<155.12	1.04 (0.60-1.80)	0.895	0.84 (0.39-1.82)	0.656
≥155.12	1.21 (0.71-2.09)	0.486	0.43 (0.15-1.24)	0.119
PNI				
<48.9	1.18 (0.67-2.08)	0.564	0.51 (0.23-1.13)	0.098
≥48.9	1.08 (0.64-1.83)	0.783	0.90 (0.32-2.56)	0.845

Table 3. Continued

	DFS		GS	
Clinicopathological characteristics	**HR (95% CI)**	**p**	**HR (95% CI)**	**p-value**
De-Ritis				
<1.091	1.85 (1.06-3.24)	0.030	0.61 (0.27-1.38)	0.238
≥1.091	0.71 (0.41-1.23)	0.222	0.67 (0.25-1.78)	0.422
CEA (ng/mL)				
<2.92	1.15 (0.64-2.07)	0.645	0.40 (0.16-1.04)	0.059
≥2.92	1.08 (0.64-1.81)	0.776	0.89 (0.39-2.06)	0.791
CA 19-9 (U/mL)				
<39.94	1.01 (0.62-1.65)	0.975	0.42 (0.18-0.99)	0.047
≥39.94	1.47 (0.79-2.73)	0.224	0.90 (0.38-2.13)	0.817
Hemoglobin (g/dL)				
<12.10	1.40 (0.80-2.47)	0.241	0.35 (0.13-0.98)	0.046
≥12.10	0.99 (0.58-1.67)	0.954	0.87 (0.39-1.93)	0.727

DFS: Disease-free survival, OS: Overall survival, HR: Hazard ratio, CI: Confidence interval, ECOG-PS: Eastern Cooperative Oncology Group Performance Status, BMI: Body mass ındex, NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, PNI: Prognostic Nutritional index, CEA: Carcinoembryonic antigen, CA 19-9: Carbohydrate antigen 19-9, HR: Hazard ratio, pT: Pathologic T

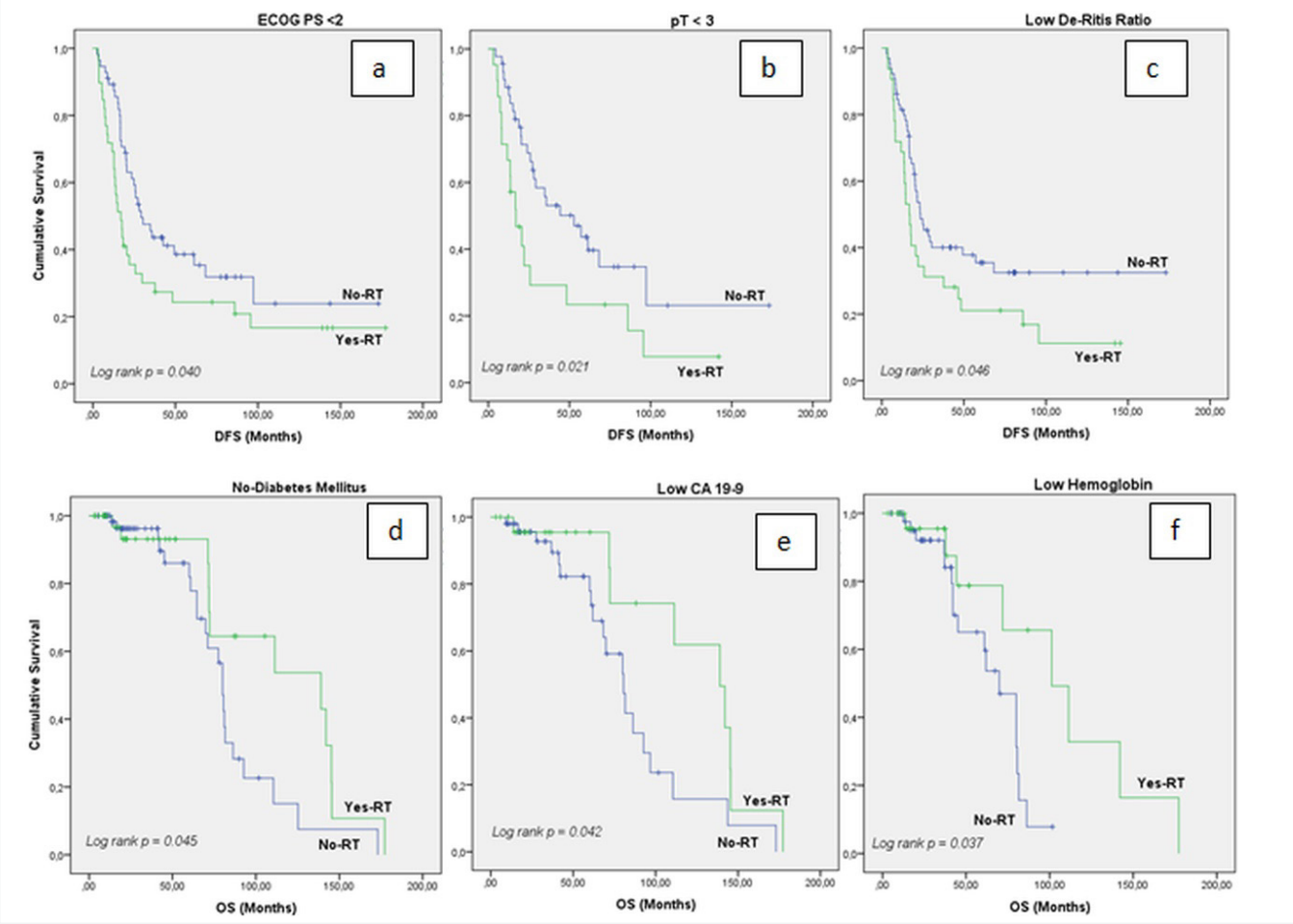

Figure 1. Comparison of survival times for patients treated with chemotherapy alone and patients treated with chemoradiotherapy in Kaplan-Meier analyses

DFS: Disease-free survival, OS: Overall survival, ECOG-PS: Eastern Cooperative Oncology Group Performance Status, pT: Pathologic T

these results. Our findings suggest that risk-based decision making and patient selection should be applied more comprehensively and carefully.

Study Limitations

Our study has some limitations. Firstly, it has a retrospective design. Secondly, although the patient selection criteria were carefully chosen, laboratory markers could still be influenced by various circumstances. Thirdly, lymph node status was significantly different for those who received CRT and those who did not receive CRT; although accurate regression analyses were performed to minimize error, this difference may have affected generalizability. Investigation of the prognostic values of some indices for CRT for the first time, including real-life data, and performing subgroup analysis are the strengths of our study. In addition, the fact that it has a multicenter design and consists of patients who all underwent optimal surgery is important for the generalizability of the results.

CONCLUSION

In conclusion, our study has shown that there are limited survival benefits of adding CRT to adjuvant chemotherapy in operated PC, and CRT candidates should be chosen carefully considering the risk of detrimental effects on some patient groups. More reasonable and optimized prospective randomized clinical trials are needed to further evaluate the benefits of RT in resectable PC.

Ethics

Ethics Committee Approval: Approval from the Non-Interventional Clinical Research Ethics Committee of Tekirdağ Namık Kemal University (TNKU) Faculty of Medicine (decision no: 2022.159.09.06, date: 27.09.2022).

Informed Consent: This study was planned as a multicenter-retrospective study and conducted in accordance with the Declaration of Helsinki.

Footnotes

Authorship Contributions

Concept: E.Ç., K.K., A.S., O.A., Design: E.Ç., K.K., Y.İ., A.S., Y.B., O.A., Data Collection or Processing: E.Ç., K.K., Y.İ., A.S., Y.B., O.A., Analysis or Interpretation: E.Ç., K.K., Y.İ., A.S., Y.B., O.A., Literature Search: E.Ç., K.K., Writing: E.Ç., K.K., O.A.

Conflict of Interest: No conflict of interest was declared by the authors.

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