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Gross tumour volume and poorly differentiated clusters can indicate high-risk patients for poor survival in pT1-2 rectal carcinomas

Gross tümör volumü ve az diferansiye kümeler pT1-2 rektal kanserlerde kötü sağkalım açısından yüksek riskli hastaları gösterebilir

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ABSTRACT

Aim: Colorectal carcinomas are one of the most common carcinomas in the Western world. Survival is mainly associated with the tumour-node-metastasis (TNM) stage but patients with the same tumour stage usually show marked distinct survival. We analyzed the survival effect of gross tumour volume and poorly differentiated clusters in pT1-2 rectal carcinomas.

Material and Method: Sixty-five pT1-2 rectal carcinomas that were curatively resected between 1999 and 2014 were included in this retrospective study at Kırıkkale University Medical Faculty Hospital. Gross tumour volume and poorly differentiated clusters were scored using a macroscopic specimen and hematoxylin and eosin-stained sections.

Results: These parameters were significantly associated with large tumour size (gross tumour volume [GTV]: p=0.020), invasive pattern (GTV: p=0.004; poorly differentiated clusters [PDC]: p=0.020), angiolymphatic invasion (GTV: p=0.001; PDC: p=0.009), tumour necrosis (GTV: p=0.002; PDC: p=0.038), and high grade (PDC: p=0.001). In univariate analysis, patients with these parameters had worse 5-year survival for both relapse-free survival (RFS) and overall survival (OS) ([GTV: RFS= 78.5%, p=0.001; OS: 81.0%, p=0.005], [PDC: RFS= 80.0%, p=0.013; OS: 83.1%, p=0.039]). Multivariate analysis confirmed that these parameters are independent predictors of poor survival for RFS (GTV: Hazard ratio [HR]=1.42 [1.06-2.85], p=0.006; PDC: HR=1.39 [1.06-3.28], p=0.028) and OS (GTV: HR=1.35 [1.09-3.37], p=0.011). Also, GTV was found to be more useful than PDC.

Conclusions: According to our study, GTV and PDC play an important role in the prognosis of rectal carcinomas and the addition of these markers to the current risk classification may contribute to better patient selection.

Keywords: Gross tumour volume, poorly differentiated clusters, rectal carcinoma, prognostic markers, pT1-2.

ÖZ

Amaç: Rektal karsinomlar batı dünyasında en sık görülen kanserlerden biridir. Hastaların sağkalımı temel olarak tümör-nod-metastaz (TNM) evresi ile ilişkilidir, ancak aynı tümör evresindeki hastalar sıklıkla belirgin farklı sağkalımlara sahiptir. Biz rektal karsinomlarda gross tümör volumü (GTV) ve az diferansiye kümeler (ADK)'in hayatta kalmaya etkilerini analiz ettik.

Gereç ve Yöntem: Kırıkkale Üniversitesi Tıp Fakültesi Hastanesi'nde 1999-2014 yılları arasında ameliyat edilen altmış beş pT1-2 rektal karsinom retrospektif olarak çalışmaya dahil edildi. GTV ve ADK kümeler makroskopi ve hematoksilen ve eozin boyalı kesitler kullanılarak skorlandı.

Bulgular: Bu parametreler büyük tümör boyutu ([GTV]: p=0,020), invasive patern (GTV: p=0,004; [ADK]: p=0,020), anjiolenfatik invazyon (GTV: p=0,001; ADK: p=0,009), tümör nekrozu (GTV: p=0,002; ADK: p=0,038) ve yüksek grade (ADK: p=0,001) ile anlamlı olarak ilişkili idi. Tek değişkenli analizde, bu iki parametreye sahip hastalar nükssüz sağkalım (NSS) ve genel sağkalım (GS) açısından 5 yıllık kötü sağkalıma sahipti ([GTV: NSS=%78,5, p=0.001; GS: %81,0, p=0,005], [PDC: NSS= %80,0, p=0,013; GS=83,1%, p=0,039]). Çok değişkenli analiz, bu iki parametrenin NSS (GTV: Hazard ratio [HR]= 42 [1,06-2,85], p=0,006; PDC: HR=1,39 [1,06-3,28], p=0,028) ve GS (GTV: HR=1,35 [1,09-3,37], p=0,011) için bağımsız kötü hayatta kalma parametreleri olduğunu doğruladı. Ayrıca, GTV'nin ADK'dan daha yararlı olduğu tesbit edildi.

Sonuçlar: Çalışmamıza göre GTV ve ADK, rektal karsinomlu hastalarda prognozda önemli bir rol oynamaktadır ve mevcut risk sınıflamasına bu belirteçleri eklemek daha iyi hasta seçimine katkıda bulunabilir.

Anahtar Kelimeler: Gross tümör volumü, az diferansiye kümeler, rektal karsinom, prognostik belirteçler, pT1-2.

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INTRODUCTION

One of the most important cancers related to death in the Western world is rectal cancers (RCs). Treatment planning for patients with RC is based on several factors, particularly the tumour-node-metastasis (TNM) stage of the tumour at the time of diagnosis (1). Only patients with pT1-2 (a tumour invading mucosa [pT1] and muscularis propria [pT2]) carcinomas are considered to have an acceptable clinical outcome without further treatment after local excision (2). Local recurrence rates of up to 25% have been reported if one or more risk factors (poorly differentiated, venous or lymphatic invasion, positive surgical margin) are reported (2,3). However, the TNM system does not take into account other evidence that allows risk classification. Therefore, it is well known that new prognostic markers are needed in addition to the current pathological staging.

Tumour measurements for size are usually determined for the longest axis and in some cases for the vertical axis. Although it is reproducible and practical, two-dimensional analysis is a bit simple and may miss many nuances that show the characteristics and extent of the disease. In some studies, it has been noted that a model defining the three dimensions of the tumour, e.g. the gross tumour volume (GTV), is more useful (4). It has been reported that the GTV can be a strong predictor of survival outcomes in many cancers, especially head and neck tumours (4). However, research on the relationship between tumour volume and prognostic factors in RC is very limited (5).

Several criteria for grading of RC have been proposed in the literature, but currently, the most widely accepted standard is defined by the degree of gland formation. Although histologic grading of tumour differentiation is an independent prognostic factor by multivariate analysis (6), there is a significant degree of interobserver variability (7). In 2012, Ueno identified poorly differentiated clustering (PDC) as an independent prognostic factor in RC patients and stated that this marker could reflect the biological aggression of RC (8,9). Therefore, GTV and PDC are promising parameters in the detection of high-risk patients.

We investigated the survival role of these parameters in pT1-2 RC cases without adjuvant chemoradiotherapy. A strong feature of our study is that it is designed in a very homogeneous population.

MATERIAL AND METHOD

Design of Study

This retrospective research was performed in a single tertiary hospital in Kırıkkale, Turkey. This study was approved by the university /local human research ethics committee and all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was carried out with the permission of Kırıkkale Üniversity Non-interventional Researchs Ethics Committee (Permission date. 26.06.2019, Decision No. 2019.05.14).

Six hundred and fifty-four patients who underwent RC surgically at the Kırıkklae University Medical Faculty Hospital between 1999 and 2014 were included in this study. In this patient population, unsuitable cases were excluded. Exclusion criteria included multiple tumours (n=4), missing tumour block (n=10), insufficient tissue in the block (n=6), advanced-stage disease (n=629), and adjuvant therapy (n=5). Finally, and our study was conducted with sixty-five pT1-2 RC cases.

Collection of Data

Diagnostic samples of cases were taken from the archives of the pathology department. Pathological, surgical, and survival information were obtained from individual records of each case. This database contains retrospectively collected data such as survival, age, invasion pattern, size, local inflammatory response, neural and vascular invasion, grade and tumour necrosis. RCs were classified according to the following criteria: Age (mean age was 73; <73 and ≥73), invasive pattern (yes and no), size (mean size was 4.5 cm; ≥4.5 cm and <4.5 cm), perineural invasion (yes and no), angiolymphatic invasion (yes and no), local inflammatory response (yes and no), tumour necrosis (yes and no) and grade (low/moderate grade and high grade). All cases were reevaluated according to the American common cancer classification committee (10). For the local inflammatory response, lymphocytes were divided into three groups (mild, moderate, intense) semiquantitatively. Tumour budding (defined as cancer clusters up to four cells at the stroma and/or tumoural border) was evaluated for invasive pattern, and cases with tumour budding greater 10 buds were considered positive for the invasive pattern.

Processing of Tissue

Paraffin-embedded archived tumour samples were obtained from sixty-five patients operated for RC between 1999 and 2014. All sections were screened for lymphovascular invasion, perineural incision and tumour necrosis. A tumour block showing the deepest invasive area was selected from each patient for PDC and sections were taken from these blocks. Cases were accepted only if sufficient tissue was present in the paraffin block for further studies. A 4 μm thickness section (n=65) was taken from each block and hematoxylin and eosin were stained (H&E). An experienced pathologist evaluated all sections.

Assessment of GTV and PDC

Information about tumour size was obtained from pathology archive records reporting the characteristics of the primary tumour. In our department, a macroscopic evaluation of primary tumour size is performed as follows. Sections of 0.3-0.5 cm thick are taken from the formalin-fixed primary tumour. From these sections, a tumour site with the largest tumour area is selected and the first two dimensions of the tumour are given relative to this section. Then, the length of each section is added, multiplied by the value above, and the final result is found. However, fresh tissue shrinks by 30% after formalin fixation (11). Therefore, this final result was normalized (Final valuesx100/70). Finally, tumour volume was classified as low GTV and high GTV according to the cut-off value associated with survival.

PDC was defined as a poorly differentiated cancer gland consisting of more than five cells in the stroma (8). Firstly, the entire tumour was examined under an x10 lens to identify the highest number of PDC areas. An area with the most prominent PDCs was then selected and the clusters were counted in an x20 objective. Finally, tumours were classified as low PDC and high PDC according to survival-related cut-off value. For the evaluation of mucinous carcinoma, tumour cell clusters with minimal extracellular mucin formation were classified as PDC, while malignant clusters in the mucin lake or large mucin pool were not considered PDC. Examples of GTV and PDC are shown in **Figure 1a-1b.**

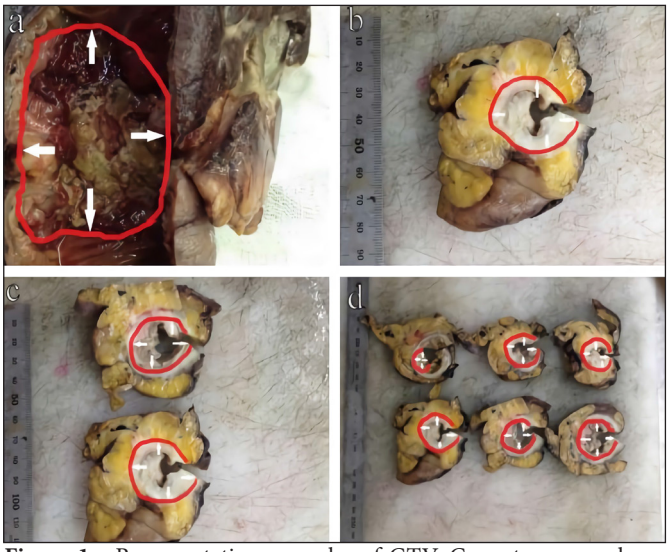

Figure 1a. Representative examples of GTV. Gross tumour volume (GTV) was evaluated in a macroscopic sample of the formalin-fixed primary tumour (a). First, 3-5 mm thick sections were taken from the tumour and two-dimensional measurements of the tumour were performed for the largest tumour area (b-c-d). This measurement was multiplied by the total cross-sectional distance and the final result was found.

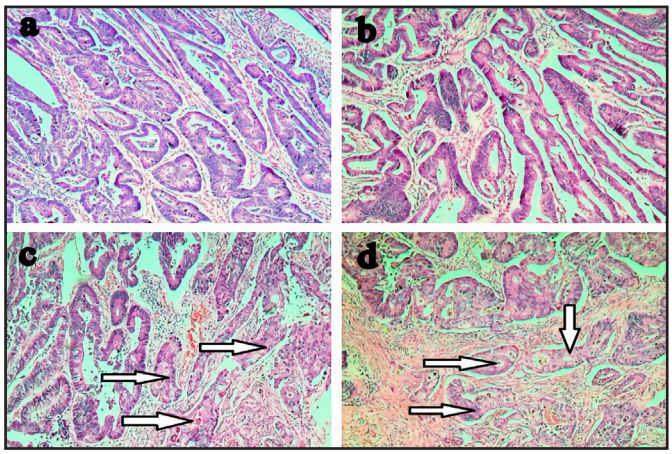

Figure 1b. Representative examples of PDC. Poorly differentiated cluster (PDC) evaluation was performed on microscopic sections of the primary tumour. First, all sections of the tumour were screened to identify the highest number of PDC sites. An area with the most prominent PDC was then selected, and clusters were counted in this area in an x20 lens. Finally, clusters were classified as low PDC (a-b) and high PDC (c-d) according to the cutoff value associated with survival.

Follow-up

In this study, outcome measures were evaluated by survival rates. Event end-point time was calculated from the day of primary surgery. To make a more reliable decision about the relapse of the patients, the follow-up period was extended and selected as 15 years. Recurrent survival (RFS) was defined as the time from primary operation day to death day for any reason or to distant or loco-regional recurrence day. General survival (OS) was the period from the day of primary operation to the day of death for any reason or to the day of the last follow-up. All events after sixty months of follow-up were censored at sixty months. Patients who developed secondary primary were excluded from survival analysis.

Statistical Evaluation

Descriptively data were noted using ranges, means and standard deviation for continuous data, and percentages and frequencies for categorical data. Chi-Square test was used to analyze the relationship between clinicopathological and categorical variables and Fisher Exact Test was performed when the Chi-Square test was not available. Spearman's correlation analysis was used for continuous data and Wilcoxon signed-rank analysis was used to investigate the differences. The optimal cut-off value related to survival was investigated by the ROC test. P-values of less than 0.05 were recorded significantly. SPSS 21.0 (IBM institute, North Castle, ABD) was used in all analyses.

RESULTS

Patients Features

Forty-two (64.6%) of the cases were male and 23 (35.4%) were female. The mean age and mean size were 73.28±7.68 (range:39-91) and 6.55±2.85 (range: 2-9), respectively. 29 (44.6%) of the tumours had an expansive pattern, 36 (55.4%) had an invasive pattern and 34 (52.3%) of the tumours were low/moderately differentiated and 31 (47.7%) were poorly differentiated. Also, survival-related cut-off value was investigated by the ROC test (GTV: ROC=70.86, AUC=0.832 [0.718-0.904]; PDC: ROC=10.56, AUC=0.824 [0.686-0.912]) and all cases were grouped as low PDC (<10 clusters) and high PDC (≥10 clusters).

Assessment of GTV and PDC

GTV was evaluated in the macroscopic specimen of the primary tumour fixed in formalin. 35 (53.8%) patients were considered as low GTV and 30 (46.2%) as high GTV. When the relationship between prognostic factors was examined, a significant relationship was found for the invasive pattern (p= 0.004), tumour necrosis (p=0.002), large size (p= 0.020), angiolymphatic invasion (p=0.001), and high grade (p= 0.001).

PDC was scored on H&E stained sections by conventional microscopy (Nikon Eclipse E600, Nikon AG Instruments, Melville, USA). The distribution of clusters was not homogeneous in slides. A suitable block with a good level of homogeneity was selected from each tumour. 35 (53.8%) patients were considered as low PDC and 30 (46.2%) as high PDC. When the relationship between prognostic factors was examined, a significant relationship was determined for the invasive pattern (p= 0.020), tumour necrosis (p=0.038), and angiolymphatic invasion (p=0.009). The relationship between GTV and PDC and clinicopathological features were shown in **Table 1**.

Follow-up

For GTV, fifteen patients died (23.0%; n=12 in high, and n=3 in low) and eighteen patients relapsed (27.6%; n=14 in high, n=4 in low). 5-year RFS and OS rates were 78.5% and 81.6% in high GTV cases and 93.9% and 95.4% in low GTV patients, respectively. For PDC, 15 patients died (23.0%; n=11 in high, and n=4 in low) and 18 patients relapsed (27.6%; n=13 in high, n=5 in low). The 5-year RFS and OS rates were 80.0% and 83.1% in high PDC cases and 92.4% and 93.9% in low PDC cases, respectively (**Table 2**).

In univariate analysis, for both GTV and PDC, significant differences were observed between survival groups for RFS (GTV: RFS, p=0.001, PDC: RFS, p=0.013) and OS (GTV: OS, p=0.005, PDC: OS, p=0.039). Invasive pattern, angiolymphatic invasion and tumour necrosis were also significantly associated with poor survival (**Table 2**, **Figure 2-3**).

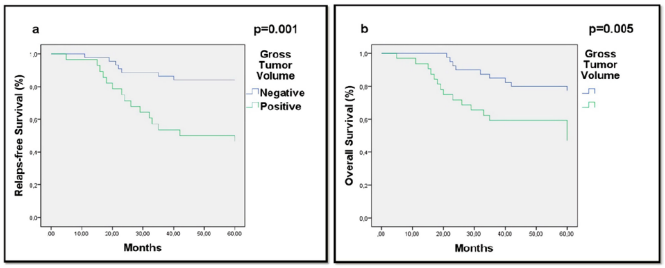

Figure 2. Kaplan-Meier survival curves of gross tumour volume P-value was significant at the 0.05 level.

Table 1. The relationship between GTV and PDC and prognostic factors (n=65)

		Gross Tumor Volume (n=65) (%)			Poorly Differetiated Cluster (n=65) (%)		
		Positive	Negative	P-value	Positive	Negative	P-value
Invasive Pattern	No	10 (34.4%)	19 (65.3%)	0.004*	11 (37.9%)	18 (62.1%)	0.020*
	Yes	25 (69.4%)	11 (30.6%)		24 (66.6%)	12 (33.4%)	
Age	<75	15 (48.3%)	16 (51.7%)	0.399	18 (58.0%)	13 (42.0%)	0.514
	≥75	20 (58.8%)	14 (41.2%)		17 (50.0%)	17 (50.0 %)	
PN invasion	No	13 (43.3%)	17 (56.5%)	0.115	14 (46.6%)	16 (53.4%)	0.282
	Yes	22 (62.8%)	13 (37.2%)		21 (60.0%)	14 (40.0%)	
Size	<5.5 cm	11 (37.9%)	18 (62.1%)	0.020*	14 (48.2%)	15 (51.8%)	0.418
	≥5.5cm	24 (66.6%)	12 (33.4%)		21 (58.3%)	15 (41.7%)	
LIR	No	14 (46.6%)	16 (53.4%)	0.282	13 (43.3%)	17 (56.7%)	0.115
	Yes	21 (60.0%)	14 (40.0%)		22 (62.8%)	13 (37.2%)	
AL invasion	No	11 (34.3%)	21 (65.7%)	0.001*	12 (37.5%)	20 (62.5%)	0.009*
	Yes	24 (72.7%)	9 (27.3%)		23 (69.6%)	10 (30.4%)	
Grade	Low/Moderate grade	12 (35.2%)	22 (64.8%)	0.001*	15 (44.1%)	19 (55.9%)	0.099
	High grade	23 (74.1%)	8 (25.9%)		20 (64.5%)	11 (35.5%)	
Tumour Necrosis	No	10 (33.3%)	20 (65.7%)	0.002*	12 (40.0%)	18 (60.0%)	0.038*
	Yes	25 (71.4%)	10 (28.6%)		23 (65.7%)	12 34.3%)	

The significance limit for the chi-square test was 0.05. The results are in italics when they are significant. Abbreviations: GTV: Gross Tumour Volume, PDC: Poorly Differentiated Cluster, PN: Perineural, LIR: Local inflammatory response, AL: Angiolymphatic

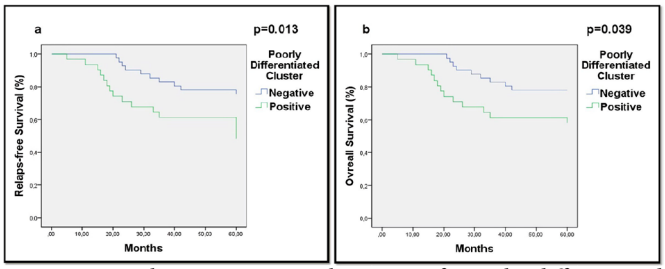

Figure 3. Kaplan-Meier survival curves of poorly differentiated cluster P-value was significant at the 0.05 level.

In multivariate analysis, GTV was an independent worse prognostic parameter for RFS (HR=1.42 [1.06-2.85], p=0.006) and OS (HR=1.35 [1.09-3.37], p=0.011). PDC was also an independent worse prognostic parameter for RFS alone (HR=1.39 [1.06-3.28], p=0.028). Angiolymphatic invasion and tumour necrosis were other parameters that were significantly associated with survival groups (**Table 2**).

DISCUSSION

The prognostic significance of GTV and PDC in curatively resected RC patients was examined in this retrospective research. According to our results, large tumour volume and poorly differentiated tumour clusters were associated with poor survival. If this evidence is confirmed by a large advanced study, these parameters can be used as a good survival marker in RC patients.

One of the most common malignant tumours in the Western world is RC. This tumour is the second most common malignant tumour among females and the third among males [12]. The TNM stage is the main guideline for the risk classification of these carcinomas. Preoperative chemotherapy is widely accepted as a standard treatment for locally advanced rectal cancer (stage T3/T4 or node-positive), whereas the standard treatment for the early disease is surgery without adjuvant therapy. However, there are many RC patients with different survival with

Table 2. Univariate and multivariate survival analysis of GTV and PDC (n=65)

		Univariate survival analysis (n=65) (%)				Multivariate survival analysis (n=65) (%)			
		OS		RFS		OS		RFS	
		5-year (%)	P value	5-year (%)	P value	HR (95% CI)	P Value	HR (95% CI)	P Value
Invasive Pattern			0.235		0.049*	-	NC	1	0.274
	No	91		83		-		3.38 (0.72-6.35)	
	Yes	85		89		-		-	
Age			0.578		0.403		NC		NC
	<77	85		85		-		-	
	≥77	91		87		-		-	
LIR			0.484		0.813		NC		NC
	No	86		80		-		-	
	Yes	90		92		-		-	
Size			0.367		0.374		NC		NC
	<5.5 cm	88		88		-		-	
	≥5.5cm	88		84		-		-	
PN invasion			0.247		0.208		NC		NC
	No	90		87		-		-	
	Yes	86		85		-		-	
AL invasion			0.045*		0.031*		0.321		0.049*
	No	93		82		1		1	
	Yes	83		90		2.56 (0.64-3.18)		1.68 (1.18-4.84)	
Grade			0.108		0.099		NC		NC
	Low/Moderate grade	92		85		-		-	
	High grade	84		87			-		-
Tumour Necrosis		0.029*		0.015*		0.041*		0.034*	
	No	94		81		1		1	
	Yes	82		91		1.53 (1.21-4.47)		1.62 (1.19-5.38)	
GTV			0.005*		0.001*		0.011*		0.006*
	Negative	95		93		1		1	
	Positive	81		78		1.35 (1.09-3.37)		1.42 (1.06-2.85)	
PDC			0.039*		0.013*		0.093		0.028*
	Low	93		92		1		1	
	High	83		80		2.27 (0.63-2.37)		1.39 (1.06-3.28)	

The significance limit for the chi-square test was 0.05. The results are in italics when they are significant. Abbreviations: GTV: Gross Tumour Volume, PN: Perineural, LIR: Local inflammatory response, AL: Angiolymphatic, NC: Not calculable, CI: Confidence interval, HR: Hazard ratio, OS: Overall survival, RFS: Relapse-free survival Survival Analyses

the same TNM stage and therefore this classification is not perfect (12). For example, it is well known that a significant proportion of advance-stage cancers never relapse and that 20-25% of early-stage cancers show adverse clinical outcomes (13). Therefore, there is a need to investigate new parameters and additional risk criteria.

While surgery remains the cornerstone of treatment in RC, there is a cautious shift toward organ-preserving strategies (14). Today, the trend towards non-surgical treatments is increasing and the optimization of neo-adjuvant strategies becomes more important. Different radiation protocols have been used in the literature showing significant differences in toxicity and response rates (14,15). In an optimal support strategy, ie low toxicity and high response, the dose level is considered as important as many factors. Today, one of the most important factors determining the dose level is GTV (15).

Improvement in the evaluation of the irregularly shaped malignant lesions is possible by measuring tumour volume. Although this can be done by analyzing digital images produced by radiological studies (16), it is more accurately correlated with volume measurements of surgical specimens (17). Also, tumour volume may provide a more accurate idea of the assessment of tumour burden and with this approach, it may be possible to further refine the different T and N categories (17). There are numerous large-scale GTV studies in head and neck cancers, and successful results for predicting survival have been reported (4). Although there are few studies in RC, significant relationships have been found (18,19). In this study, we found that high GTV is an independent prognostic factor for poor RFS in RC. If more comprehensive studies are conducted on this finding, more successful results can be obtained in adjuvant therapies.

By definition, PDC is a group of poorly differentiated tumour cells larger than tumour budding, which can be easily evaluated in HE sections (20). In terms of survival outcomes, the PDC number-based tumour grading system may classify patients as more efficient than a system based on loss of gland formation (20). For example, medullary carcinoma classified as Grade 3 according to World Health Organization criteria and TNM classification has a positive prognosis. This finding demonstrates that the biological aggression of a tumour is reflected in PDC production rather than the gland loss phenomenon, which is thought to be a feature of Grade 3 tumours (20,11).

Different assessment methods have been used in the literature and therefore there is no standard reporting for PDC (21). Most studies divide the PDC into 3 degrees by the number of PDCs in an x20 objective, while some studies have used the presence/absence of PDC (21,22). In this study, we used an x20 objective in the evaluation and found the survival-related cut-off value to be 10 clusters. However, the presence of PDC in 5-year OS was not statistically significant. This difference may be due to the limited number of cases in our study. Further studies are needed on this subject.

There are some limitations to this study. First, there is a limitation in the nature of retrospective research. In our study, cases were treated with previous guidelines before 2013, which produced the distinction between studies that have been treated for RC today. We investigated GTV and PDC in one block and we know that it symbolizes a small part of the whole tumour. Nevertheless, this study is the largest in the literature investigating GTV and PDC in early-stage rectal cancer in our country.

CONCLUSION

Large tumour volume and a large number of poorly differentiated tumour clusters were associated with poor survival in our study. Therefore, these parameters can be a good predictor for poor prognosis in RC patients. Also, these markers can be very useful in identifying high-risk patients when deciding adjuvant therapy in early-stage RC patients.

Abbreviations

RC: Rectal carcinoma, **AJCC**: American Joint Cancer Committee, **GTV**: Gross Tumour Volume, **PDC**: Poorly Differentiated Cluster, **HPF**: High power field, **H&E:** Hematoxylin and eosin, **SD**: Standard deviation, **HR**: Hazard ratio, **OS**: Overall survival, **RFS**: Relapse-free survival

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kırıkkale Üniversity Non-interventional Researchs Ethics Committee (Permission date. 26.06.2019, Decision No. 2019.05.04).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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