Original Article – Urologic Oncology

Prognostic Value of Computed Tomography Urography Contrast Enhancement in Predicting Grade and Muscle Invasion in Bladder Cancer

Bilgisayarlı Tomografi Ürografide Kontrastlanma Miktarının Mesane Kanserinde Tümör Derecesini ve Kas İnvazyonunu Tahmin Etmedeki Prognostik Değeri

Short Title: CT Urography Contrast Enhancement of Bladder Cancer (BT Ürografide Mesane Kanseri Kontrast Tutulumu)

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Abstract

Objective: This study aimed to investigate the relationship between contrast enhancement on computed tomography (CT) urography and tumor grade, recurrence, and muscle invasion in patients who underwent CT urography for hematuria and were found to have bladder tumors.

Materials and Methods: A total of 70 patients diagnosed with bladder cancer between February 2022 and February 2023 were prospectively included in the study. Preoperative CT urography was performed in all patients. Hounsfield unit (HU) measurements were obtained from the tumor in both non-contrast and nephrographic phases. The difference between these values was defined as the contrast enhancement level. The association between contrast enhancement and tumor grade, recurrence, and muscle invasion was statistically analyzed.

Results: High-grade bladder tumors were identified in 46 patients, while 24 had low-grade tumors. The contrast enhancement values were significantly higher in high-grade tumors compared to low-grade tumors (28.9 ± 11.8 HU vs. 17 ± 10.3 HU, $p < 0.01$). Among the 16 patients who experienced tumor recurrence, the enhancement values were significantly higher than those without recurrence (30.3 ± 10.5 HU vs. 23.2 ± 12.8 HU, $p < 0.05$). In cases of muscle-invasive tumors, contrast enhancement levels were significantly higher than those in non-muscle-invasive tumors (41.75 ± 4.8 HU vs. 22.6 ± 11.6 HU, $p < 0.01$). ROC analysis revealed a threshold value of 19.5 HU for distinguishing high- and low-grade tumors (sensitivity: 80%, specificity: 75%), and 36 HU for detecting muscle invasion (sensitivity: 100%, specificity: 84%). According to the multivariate logistic regression analysis, contrast enhancement was identified as an independent risk factor for high-grade bladder tumors (OR = 1.09, 95% CI: 1.031–1.152, $p = 0.02$).

Conclusion: The amount of contrast enhancement observed in preoperative CT urography of bladder tumors may serve as a useful imaging biomarker for assessing tumor aggressiveness and preoperative risk stratification.. Further studies with larger patient cohorts are needed to validate these findings.

Keywords: bladder cancer, CT urography, contrast enhancement, tumor grade, muscle invasion, prognosis

Özet

Amaç: Çalışmanın amacı, hematüri nedeniyle preoperatif dönemde gerçekleştirilen bilgisayarlı tomografi (BT) -ürografi incelemesinde mesane tümörlerinin kontrast tutulum düzeyinin; tümör derecesi, tümöral nüks ve kas invazyonu ile ilişkisini değerlendirmektir.

Gereçler ve Yöntemler: Şubat 2022 – Şubat 2023 tarihleri arasında mesane kanseri tanısı almış 70 hasta prospektif olarak çalışmaya dahil edildi. Tüm hastalara preoperatif BT-ürografi uygulandı. Kontrastsız ve nefrogram fazlarındaki görüntülerde, mesane tümöründen Hounsfield unit (HU) cinsinden ölçümler yapıldı. Bu iki değer arasındaki fark kontrast tutulum miktarı olarak tanımlandı. Elde edilen veriler, tümör derecesi (yüksek/düşük), nüks gelişimi ve kas invazyonu ile istatistiksel olarak karşılaştırıldı.

Bulgular: Yüksek dereceli tümör tespit edilen 46 hastada kontrast tutulum değeri, düşük dereceli 24 hastaya kıyasla anlamlı derecede daha yüksek bulundu (28.9 ± 11.8 HU vs. 17 ± 10.3 HU; $p < 0.01$). Tümöral nüks gelişen 16 hastada kontrastlanma miktarı, nüks gözlenmeyen hastalara göre anlamlı düzeyde daha yüksekti (30.3 ± 10.5 HU vs. 23.2 ± 12.8 HU; $p < 0.05$). Kas invaziv tümörlerde kontrast tutulum değeri, yüzeyel tümörlere göre anlamlı derecede yüksek bulundu (41.75 ± 4.8 HU vs. 22.6 ± 11.6 HU; $p < 0.01$). ROC analizi sonucunda; yüksek ve düşük dereceli tümörleri ayırt etmede 19.5 HU (duyarlılık: %80, özgüllük: %75), kas invazyonunu ayırt etmede ise 36 HU (duyarlılık: %100, özgüllük: %84) eşik değerleri saptandı. Çok değişkenli lojistik regresyon analizine göre, kontrast tutulumu yüksek dereceli mesane tümörleri için bağımsız bir risk faktörü olarak saptanmıştır (OR = 1.09, %95 GA: 1.031–1.152, $p = 0.02$).

Sonuç: Mesane tümörlerinde BT-ürografi tetkiki ile saptanan kontrastlanma miktarı, tümör derecesi ve kas invazyonu ile anlamlı ilişki göstermektedir ve nüks gelişen hastalarda daha yüksek değerler izlenmiştir. Daha geniş hasta serileri ile yapılacak ileri düzey çalışmalar, bu yöntemin cerrahi öncesi risk sınıflamasında biyogösterge olarak kullanımını destekleyebilir.

Anahtar kelimeler: mesane kanseri, BT ürografi, kontrast tutulum, tümör derecesi, prognoz

Introduction

Bladder cancer is the tenth most common malignancy worldwide and is associated with a high mortality rate if left untreated [1]. It is classified into two major categories: non-muscle invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC), with NMIBC accounting for the majority of cases. NMIBC includes mucosa-limited (pTa), lamina propria-invasive (pT1), and carcinoma in situ (CIS) stages. If untreated, approximately 50% of NMIBC cases progress to MIBC. Additionally, the recurrence rate after treatment remains high, ranging from 70% to 80% [2].

Ultrasonography (USG) and computed tomography (CT) urography are commonly used for the diagnosis of urinary tract pathologies. While USG is useful for detecting intra-bladder tumors, assessing hydronephrosis, and characterizing renal tumors, it is limited in its ability to identify upper urinary tract tumors [3]. CT urography is typically performed in three phases: the non-contrast phase, the nephrographic phase (with an 80–120 second delay), and the excretory phase (with a 10–15 minute delay) [4]. It is highly sensitive for detecting renal masses and identifying filling defects within the urinary collecting system [5,6].

Neoplastic tissues are known to exhibit high vascularization to support proliferation and maintain viability [7]. The angiogenic activity of malignant tissues is believed to have prognostic significance. Studies assessing the vascularization of bladder and renal pelvis tumors have demonstrated an association between tumoral vascularization and tumor grade, stage, and prognosis [8,9]. In these studies, vascularization was typically evaluated using immunohistochemical staining, vessel quantification, or contrast-enhanced imaging techniques [10-13].

Contrast enhancement techniques have emerged as valuable methods for assessing bladder cancer, offering insights into tumor aggressiveness and aiding in staging and grading. Contrast-enhanced ultrasound (CEUS) has been explored for its diagnostic accuracy in differentiating between muscle-invasive and non-muscle-invasive bladder cancer, offering a cost-effective and safe imaging alternative [14,15]. Contrast enhancement observed in CT urography has been demonstrated to correlate with tumor vascularization and histological grade [13].

This study aimed to assess the prognostic significance of contrast enhancement in CT urography for bladder cancer.

Materials and Methods

Patients

Between February 2022 and February 2023, a total of 78 patients who presented with hematuria and were subsequently diagnosed with bladder tumors on CT urography were prospectively evaluated. Preoperative CT urography was performed in all patients, and tumor characteristics, including tumor size and contrast enhancement, were measured prior to surgical intervention and pathological evaluation.

Patients with contrast allergy (n=3), those whose pathology results indicated papilloma (n=2), and those who underwent single-phase intravenous contrast-enhanced CT (n=3) were excluded from the study. Consequently, 70 patients who met the inclusion criteria were included in the final analysis.

CT measurements were performed using contrast-enhanced CT urography images obtained before surgery. The degree of contrast enhancement of the bladder tumor was recorded and later compared with the pathological tumor grade obtained after transurethral resection of the bladder tumor (TURBT).

Patients were followed postoperatively through routine cystoscopic surveillance for tumor recurrence. For the purpose of analysis, patients who developed tumor recurrence within the first 12 months of follow-up were recorded as recurrence cases.

Written informed consent was obtained from all patients. Ethical approval was granted by the local ethics committee (Decision No: 12, Protocol No: 2021/193).

CT Urography Protocol and Measurement of Contrast Enhancement

All CT scans were obtained using a 128-detector CT scanner (Aquilion Prime, Toshiba Medical Systems, Otawara, Japan). All patients were instructed to consume 500 mL of water one hour before the CT scan to ensure adequate bladder distension. Following the acquisition of the non-contrast phase, 100 mL of a non-ionic contrast agent (Opaxol 350 mg/mL) was administered intravenously. Nephrographic phase images were acquired at 70 seconds, while pyelographic phase images were obtained at 300 seconds.

CT attenuation measurements were performed on preoperative CT urography images prior to surgical intervention and pathological evaluation. Attenuation values of the bladder tumors were measured in Hounsfield units (HU) at the non-contrast and nephrographic phases using regions of interest (ROI). Attenuation was assessed on a single axial image at the level of the maximum tumor diameter. The largest possible circular ROI was placed at the center of the tumor to minimize partial volume effects and to avoid including the surrounding bladder wall or urine (**Figure 1**).

All measurements were performed by a radiologist who was blinded to the pathological results. Each measurement was performed twice in two separate sessions, and the mean value of the two measurements was used for the final analysis. The difference between the attenuation values obtained from the nephrographic and non-contrast phases was defined as the CT enhancement value.

Statistical Analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) version 25.0 software (IBM Corporation, Armonk, NY, USA). The normality of the data distribution was assessed using the Shapiro–Wilk test. The relationship between CT enhancement values and tumor grade was analyzed using the Mann–Whitney U test. Receiver operating characteristic (ROC) analysis was performed to determine the optimal cut-off value.

Multivariate logistic regression analysis was performed to identify independent predictors of high-grade urothelial carcinoma. Variables included in the multivariate model were selected based on their clinical relevance and the objective of the study, which was to evaluate the predictive value of preoperative CT urography findings. To reduce the risk of model overfitting given the relatively limited sample size, the number of variables included in the model was restricted.

Data were presented as mean ± standard deviation. All variables were analyzed with a 95% confidence interval, and a p value <0.05 was considered statistically significant.

Results

Of the 70 patients included in the study, 46 were diagnosed with high-grade (HG) and 24 with low-grade (LG) urothelial carcinoma. A total of 62 patients were diagnosed with NMIBC, while 8 patients were diagnosed with MIBC. The cohort consisted of 64 male and 6 female patients, with a mean age of 66.8 ± 10 years. The mean age was significantly higher in the high-grade group (69.3 ± 9 years) compared to the low-grade group (62 ± 9.9 years) ($p <0.01$). Additionally, the mean tumor size was significantly larger in the high-grade group (37 ± 21 mm) than in the low-grade group (21.5 ± 14 mm) ($p <0.01$) (**Table 1**).

The mean CT enhancement value was 28.9±11.8 HU in the high-grade group and 17±10.3 HU in the low-grade group. Contrast enhancement was found to be significantly higher in the high-grade group compared to the low-grade group ($p <0.01$). Tumor recurrence was observed in 16 patients, while 54 patients had no recurrence. The mean CT enhancement value was 30.3±10.5 HU in the recurrence group and 23.2±12.8 HU in the non-recurrence group. Tumor contrast enhancement was significantly higher in patients with recurrence ($p <0.05$) (**Table 2**).

ROC curve analysis demonstrated that the degree of contrast enhancement in bladder tumors could effectively differentiate between high-grade and low-grade urothelial carcinoma.

Using the Youden Index, the optimal cut-off value for CT enhancement was determined to be 19.5 HU, with a sensitivity of 80% and a specificity of 75% (AUC: 0.76, p <0.01, 95% CI: 0.635–0.885) (**Figure 2**).

The mean contrast enhancement was 41.75±4.8 HU in patients with muscle-invasive bladder cancer and 22.6±11.6 HU in patients with superficial bladder cancer. Contrast enhancement was significantly higher in the muscle-invasive group. ROC curve analysis indicated that contrast enhancement on CT urography can effectively differentiate between muscle-invasive and superficial bladder cancer. The optimal cut-off value for CT enhancement was 36 HU, with a sensitivity of 100% and a specificity of 84%. (AUC: 0.927, p <0.01, 95% CI: 0.865–0.990) (**Figure 2)**. The demographic data and contrast enhancement characteristics of patients with invasive and superficial bladder cancer are summarized in **Table 3**.

A multivariate logistic regression model was constructed to identify independent predictors of high-grade tumors. Contrast enhancement, age, gender, and tumor size were included as covariates in the model. The results demonstrated that both contrast enhancement and age were independently associated with high-grade tumors (OR = 1.09, 95% CI: 1.031–1.152, p = 0.02; OR = 1.081, 95% CI: 1.007–1.160, p = 0.03, respectively).

A separate multivariate logistic regression model was constructed to identify predictors of tumor recurrence. Tumor grade, tumor number (solitary vs. multiple), tumor size, and contrast enhancement were included as covariates. In this analysis, tumor number emerged as an independent risk factor for recurrence (OR = 7.979, 95% CI: 2.004–31.766, p <0.01).

Discussion

Accurate grading and staging of bladder cancer and the assessment of prognostic factors play a critical role in guiding urologists in selecting the appropriate surgical and postoperative treatment strategies. Low-grade bladder cancer, characterized by slow progression and lower malignant potential, is typically treated with TURBT, often followed by intravesical therapy with agents such as mitomycin and epirubicin. In contrast, high-grade and muscle invasive bladder cancer frequently requires radical cystectomy, with postoperative Bacillus Calmette–Guérin (BCG) therapy or more intensive treatment approaches [16,17]. Tumor stage and histopathological grade are the most critical prognostic factors influencing the survival of bladder carcinoma [18].

Understanding the biological behavior of the disease is crucial for selecting the most appropriate treatment modality and optimizing patient outcomes. Therefore, differentiating the tumor grade and histopathological stage of bladder urothelial carcinoma is essential for optimizing patient management and improving clinical outcomes.

CT urography is widely utilized for its high diagnostic accuracy in evaluating the etiology of hematuria and detecting bladder tumors [19]. There is currently no universally accepted standard protocol or established national and institutional guidelines for CT urography, leading to significant variability in acquisition techniques and contrast administration protocols [20,21]. CT urography is typically performed in three phases: a non-contrast phase, a nephrographic phase acquired 80–120 seconds after contrast administration, and an excretory phase obtained 5–15 minutes post-injection [22]. Maximum contrast enhancement of bladder tumors has been observed between 60 and 80 seconds after contrast agent administration [23].

In line with previous studies using contrast-enhanced imaging, our findings demonstrate that contrast enhancement in bladder cancer may help differentiate between low- and high-grade tumors and serves as an independent predictor of high-grade disease.

Studies evaluating contrast enhancement of bladder tumors using CT urography are limited. The predictive value of tumor contrast enhancement has mostly been investigated using contrast-enhanced ultrasonography. Previous studies have demonstrated that CEUS can effectively differentiate between high-grade and low-grade bladder tumors [24,25]. Nevertheless, contrast-enhanced ultrasonography has been shown to be a useful tool in the T staging of bladder cancer and may aid in the detection of muscle invasion [26,27].

Tumor tissues typically demonstrate greater vascularization than normal tissues, which supports tumor proliferation and sustains cellular survival. Accumulating evidence indicates that the progression and metastatic potential of tumors are closely related to their ability to promote neovascularization [28]. Previous studies have shown that microvessel density is associated with tumor aggressiveness [29]. Malignant tissues often demonstrate greater contrast enhancement than normal tissues in contrast-enhanced imaging, which is largely attributed to increased tumor vascularization. The formation of new blood vessels results in physiological alterations, including elevated perfusion, increased blood volume, and greater capillary permeability, all of which influence the degree of contrast enhancement observed on computed tomography [30].

Previous studies have suggested that contrast enhancement characteristics obtained from imaging modalities may reflect the biological behavior of tumors. Cai Feng Wan et al. proposed that the contrast enhancement pattern observed on contrast-enhanced ultrasound in patients with breast cancer could serve as a non-invasive biomarker of tumor characteristics [31]. Similarly, in a study evaluating contrast-enhanced ultrasound in prostate cancer patients, peak intensity values were found to be significantly associated with gleason score and microvessel density (MVD). These findings support the concept that imaging-based contrast enhancement parameters may indirectly reflect tumor vascularity and aggressiveness. Consistent with these observations, our study demonstrated that contrast enhancement values obtained from CT urography were associated with tumor grade and recurrence in bladder cancer patients [32].

Studies investigating the role of CT urography in the diagnosis of bladder cancer have shown that it can be used with high accuracy for detecting bladder cancer [33,34]. In the study conducted by Xie et al., contrast enhancement observed on contrast-enhanced CT in bladder cancer was reported to show a positive correlation with tumor grade and MVD [13]. In a meta-analysis investigating MVD as a prognostic marker in bladder cancer, high microvessel density was found to be associated with poor survival outcomes, suggesting its potential role as a prognostic indicator [35].

From a clinical perspective, imaging markers that provide information about tumor aggressiveness before surgery may contribute to improved risk stratification and treatment planning in patients with bladder cancer. Preoperative assessment of contrast enhancement on CT urography may help clinicians anticipate the likelihood of high-grade disease or muscle invasion and may assist in guiding clinical decision-making and follow-up strategies. However, further prospective studies with larger patient populations are required to confirm the clinical utility of CT enhancement as a prognostic imaging biomarker.

The 2006 European Organisation for Research and Treatment of Cancer (EORTC) scoring model predicts short- and long-term recurrence and progression risks in bladder cancer based on six key factors: number of tumors, tumor size, prior recurrence rate, T category, presence of concurrent CIS, and World Health Organization (WHO) 1973 tumor grade [36]. Predicting recurrence and progression in bladder cancer may contribute to the personalization of treatment and follow-up strategies, potentially reducing unnecessary cystoscopies in low-risk patients while enabling closer surveillance in high-risk cases.

In the present study, contrast enhancement values were higher in patients who developed tumor recurrence. However, in the multivariate logistic regression analysis, tumor number emerged as the only independent predictor of recurrence. This finding suggests that the association between contrast enhancement and recurrence observed in the univariate analysis may be influenced by other clinicopathological factors. Therefore, contrast enhancement alone may not be sufficient to serve as an independent prognostic biomarker for recurrence. These findings should be interpreted with caution, and further studies with larger patient cohorts are warranted to better clarify the potential prognostic role of CT contrast enhancement in predicting bladder tumor recurrence.

Taken together, the findings of this prospective study suggest that contrast enhancement measured on CT urography may provide valuable information about the biological behavior of bladder tumors. Higher enhancement values were associated with high-grade disease and muscle invasion, supporting the concept that imaging-based vascular characteristics may reflect tumor aggressiveness. As CT urography is already widely used in the evaluation of hematuria, quantitative assessment of contrast enhancement may offer an additional non-invasive parameter for preoperative risk assessment. Nevertheless, further prospective studies with larger patient populations are required to validate these findings and to determine the potential role of CT enhancement parameters in clinical decision-making.

The present study has several limitations. First, the number of patients with muscle-invasive bladder cancer was relatively small, which may limit the generalizability of the findings regarding muscle invasion. Second, this was a single-center study with a limited sample size, which may introduce potential selection bias. Third, CT attenuation measurements were performed by a single radiologist; although measurements were repeated in two separate sessions and the mean value was used for analysis, interobserver variability could not be evaluated. Finally, the use of a single ROI measurement from the tumor center may not fully reflect the potential heterogeneity of bladder tumors.

Conclusion

Contrast enhancement on CT urography was significantly associated with tumor grade and showed higher values in patients with recurrence. While it independently predicted high-grade disease, it was not identified as an independent predictor of recurrence. These findings suggest that contrast enhancement may serve as a useful imaging marker for tumor aggressiveness.

Ethics Committee Approval: This study was approved by the Aydın Adnan Menderes University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee (Decision No: 12, Protocol No: 2021/193).
Informed Consent: Written informed consent was obtained from all patients.
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Table 1. Comparison of the groups based on tumor size and demographic characteristics

	Age	Tumor size (mm)	Gender Men Women
Low grade (LG) (%) N=24	62±9.9	21.5±14	22 (%91.6) 2 (%8.4)
High grade (HG) (%) N=46	69.3±9	37±21	42 (%91.3) 4 (%8.7)
P	**<0.01**	**<0.01**	0.6

Table 2. Association of contrast enhancement in CT urography phases with tumor grade and recurrence status

	High grade **n: 46**	**Low grade** **n: 24**	**p**	**Recurrence** **n: 16**	**Recurrence free** **n: 54**	**P**
Non-contrast phase attenuation (HU)	33.9±11.1	30.25±9.2	0.18	28.7±8.1	33.8±11	0.13
Nephrogram phase attenuation (HU)	62.9±12.1	47.2±12.5	<**0.05**	59.1±9.2	57±15.5	0.14
CT enhancement value (HU)	28.9±11.8	17±10.3	**<0.01**	30.3±10.5	23.2±12.8	**<0.05**

Table 3. The Demographic data and contrast enhancement characteristics of patients with invasive and superficial bladder cancer

	Age	Tumor size (mm)	Gender Men Women	CT enhancement value (HU)
Superficial (%) N=62	66.3±10.3	28.8±19.3	56 (%90.4) 6 (%9.6)	22.6±11.6
Invasive (%) N=8	70.5±5.3	54.7±12.9	8 (%100) 0	41.75±4.8
P	**P<0.09**	**P<0.01**	0.35	**P<0.01**

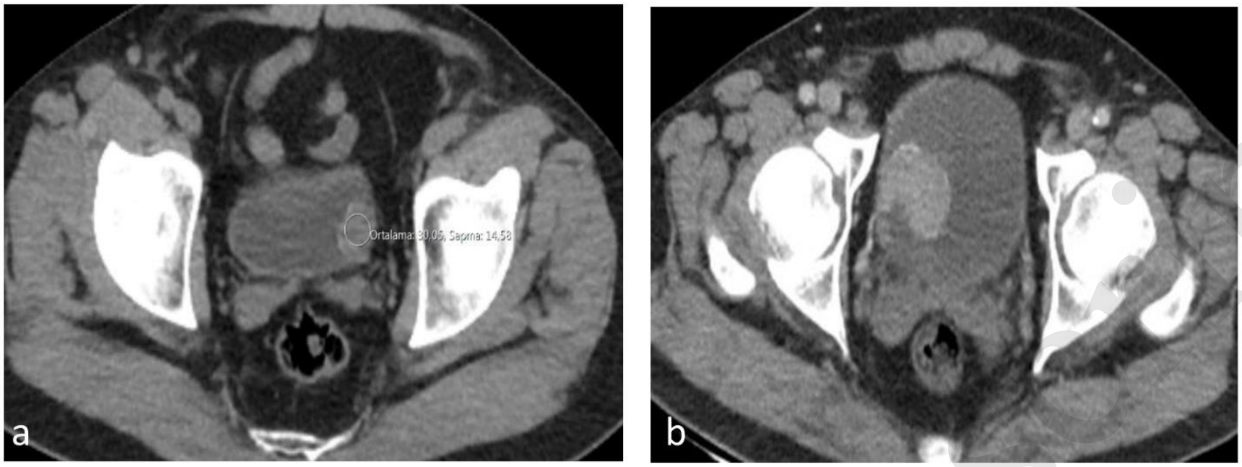

Figure 1. Acquisition of axial images and measurements of contrast enhancement of bladder tumors in (a) non-contrast and (b) nephrographic phases

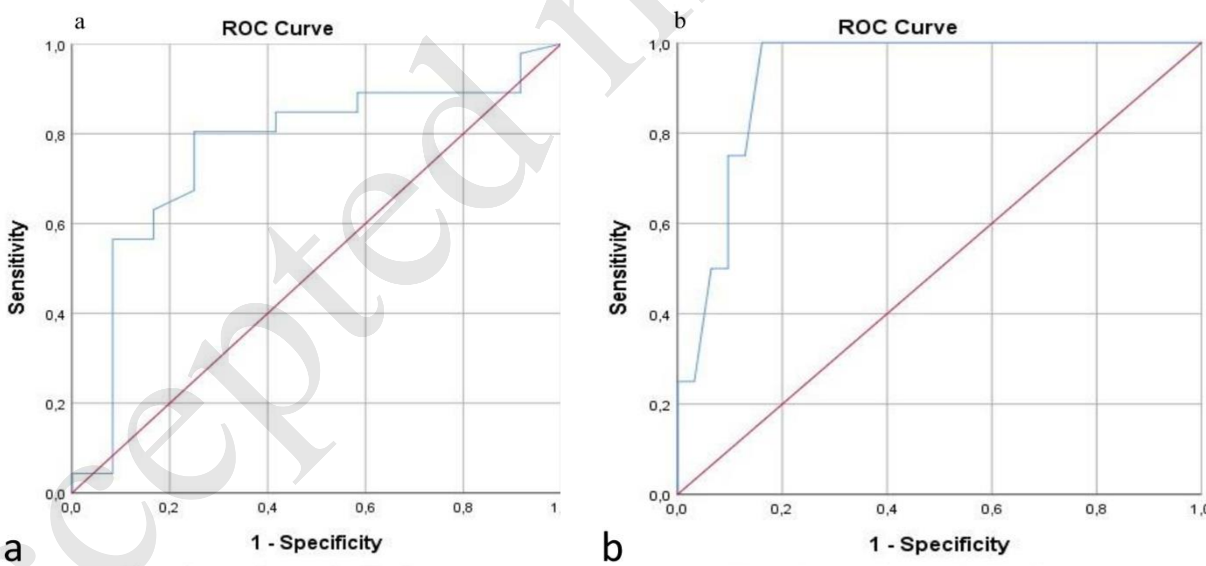

Figure 2. a) ROC curves for differentiation of low- and high-grade bladder cancer with mean CT enhancement value b) ROC curves for differentiation of invasive and superficial bladder cancer with mean CT enhancement value