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Original Research

The Significance of Preoperative Computed Tomography Features in the Prediction of Overall Survival in Gastric Cancer: A Retrospective Analysis

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Abstract

Objectives: Computed tomography (CT) is a frequently used modality for staging in the preoperative evaluation of gastric cancer (GC). Our aim was to interpret the importance of preoperative CT features in predicting overall survival (OS) in patients operated for GC.

Methods: One hundred and one patients with GC (33 women, 68 men; range of age: 29–82 years, median age: 61 years) who had abdominal CT prior to surgical resection were included in the study retrospectively. Two radiologists evaluated CT scans to record the longest dimension of the tumor, the localization of the lesion, the attenuation values of the tumor in the arterial and venous phases (Hounsfield units), invasion depth of the lesion (T stage), and the number of pathological lymph nodes (LNs) (N stage). Postoperative pathological results including resection (R0, R1), T stage, N stage, grade, and histopathological subtype were documented. All CT-provided results and clinicopathological features associated with OS were analyzed by univariate, multivariate, and receiver operator characteristic analysis.

Results: Multivariate analysis revealed that none of the CT features were associated with the OS. After resection, the survival ratio was poor for the R1 and high-grade groups than for the R0 and low-grade groups (p=0.001 and p=0.005, respectively). N stage and the longest dimension of the tumor on CT imaging truly estimated R1 resection status (AUC, 0.697; sensitivity, 63%; and specificity, 88%, and AUC, 0.734; sensitivity, 18%; and specificity, 76%, respectively).

Conclusion: R1 resection status is associated with poor OS in GC. CT features, including the tumor's longest dimension and the number of pathological LNs, can predict R1 resection status.

Keywords: Computed tomography, gastric cancer, grade, radiology, resection, survival

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Gastric cancer (GC) is the fifth common malignancy (5.6% of all cancers) and the fourth reason of canc er-related deaths around the world.[1] The current curative treatment of GC is surgery, including partial or total resection of the stomach combined with lymphadenectomy.[2] Multidisciplinary treatment options such as neoadjuvant chemotherapy and radiotherapy, perioperative chemotherapy, and adjuvant chemotherapy are supported to make better the

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clinical benefit rate of GC patients by improving the chance of radical tumoral resection, disease-free survival (DFS), and overall survival (OS).[3,4] However, despite these increased treatment options and good treatment responses, OS is still very low in some patients.[5,6] Thus, there is a need for clinical and radiological findings that will predict the patient's outcome before starting treatment and operation.

Computed tomography (CT) is a frequently used modality for staging in the preoperative evaluation of GC. CT can detect the tumor's anatomical and morphological details, its local spread, and pathological lymph nodes (LNs) because of the multiplanar reconstruction techniques and high spatial resolution. The prognostic factors for predicting recurrence are vascular invasion, serosal invasion, and metastasis to the LNs.[7-10] Many studies investigated the presence of these findings in CT examination and their correlation with postoperative findings. One study showed that preoperative CT could select high-risk patients in neoadjuvant therapy decisions by measuring CT tumor depth and tumor size.[11] A recently published study showed that CT's sensitivity for LN metastasis of advanced GC was as high as 90%. However, the specificity was as low as 47%.[12] Dynamic CT examination reveals the neovascularization of the tumor and contributes to the assessment. Komori et al.[13] reported the correlation between tumor neoangiogenesis and lymphatic vessel invasion with the extent of the tumoral enhancement in the arterial phase of CT. They concluded extent of tumor enhancement was a good and independent prognostic factor after curative resection. Yin et al.[14] showed the correlation between contrast enhancement ratio of the arterial phase and microvascular invasion in GC. Ma et al.[15] published a study in 2016 and showed that dynamic CT could be a non-invasive method to predict lymphovascular invasion in advanced GC due to quantitative enhancement measurement. As mentioned above, CT findings were compared with pathological findings and prognostic criteria in previous studies. There are relatively few studies investigating the correlation of morphological and dynamic CT findings with survival in operated GC.

The purpose of our research was to analyze the importance of morphological and dynamic preoperative CT features in predicting OS in patients operated for GC.

Methods

Patient Population

The study protocol was approved by our institutional ethics committee number with July 02, 2020–109412 and has been conducted in accordance with the Helsinki Declaration of principles. Informed consent was waived due to the retrospective nature of the study. We retrospectively evaluated the medical archives of our institute. Patients who underwent surgery for GC in our hospital between 2010 and 2019 were recorded. One hundred and fifty-six patients with (pT1–T4 stage) who underwent preoperative staging with dynamic CT and subsequent surgical resection were enrolled in this study. Patients who had not sufficient CT image and clinicopathological data or were lost to follow-up, underwent palliative surgery, or underwent neoadjuvant chemotherapy were excluded from the study. Finally, 101 patients with GC (33 women, 68 men; range of age: 29–82 years, median: 61 years) who had adequate dynamic CT imaging prior to surgical resection were included in the study.

CT Protocol

All patients underwent scanning with a 64-detector CT scanner (Aquilion 64, Toshiba Medical Systems, Tochigi, Japan). Scanning covered the entire upper and lower abdomen during a single breath-hold patient with supine position. Arterial phase CT images were received at 40 s, and venous phase CT images were received 70 s after injecting 2 mL/kg of nonionic contrast agent (iopamidol, Iopamiron 370, Bayer Schering Pharma) at a rate of 3 mL/s. All CT images were transferred to a workstation adapted with image reconstruction software (ExtremePacs).

Image Review

Two radiologists with seven and more than 20 years of experience evaluated preoperative CT images in consensus. Both radiologists were blinded to pathology results and clinical information of patients. Tumor invasion depth, pathological LN status (number of pathological LN), the longest diameter of tumor, location of the tumor, and Hounsfield unit (HU) in arterial and venous phases were evaluated with preoperative dynamic CT images. T stage (tumor depth) was categorized into three groups as follows: T1-T2, T3, and T4. The T1-T2 group was defined when transmural involvement was not seen. The T3 group was defined when transmural involvement was present, and the tumor reached the serosa without invasion of the adjacent tissues, and the T4 group was defined as tumor invaded serosa and adjacent tissues. According to the preoperative N staging, pathological LNs were categorized into four groups: N0, N1, N2, and N3 using the latest 8th International Union Against Cancer (UICC) TNM Staging System.[16] CT imaging criteria for metastatic LNs were similar to a previous study.[17] The LNs, which had a short-axis diameter greater 8 mm, were round in shape, and had a central hypodensity secondary to the necrosis or settled in a cluster (three nodes or more), were con-

sidered to be metastatic. The longest diameter of the tumor was measured on the coronal or axial plane and was classified into four categories: (1) <3 cm, (2) 3–6 cm, (3) 6–9 cm, and (4) more than 9 cm. The tumor's location was classified as cardia, fundus, corpus, greater curvature, minor curvature, antrum, esophagogastric junction, and more than one location. HUs were measured in arterial and venous phases by setting a region of interest (ROI) at the tumor site avoiding the necrotic components. The minimal, maximal, and mean attenuation values were automatically calculated and recorded. Mean values were categorized into three groups as follows: (1) <40, (2) 40–60, and (3) more than 60 for both arterial and venous phases (Fig. 1).

Pathologic Evaluation

Histopathological subtype (tubular, papillary, tubulopapillary, mucinous, signet ring cell carcinoma, intestinal, diffuse, adenosquamous, subtype not specified), pathologic T stage (pT1-T4), N stage (N0-3), grade (grade 1–3), lymphovascular invasion, location of the tumor (cardia, fundus, corpus, great curvature, small curvature, antrum, more than one location), resection status (R0, R1), type of operation (total, subtotal gastrectomy), type of LN dissection (D1, D2) were retrieved from the pathology reports.

Statistical Analysis

OS was described as the time from diagnosis to the last follow-up visit. Survival status at the last control were recorded. OS was evaluated by using the Kaplan–Meier method. All CT-provided features and clinic and pathological features associated with OS were analyzed by univariate and multivariate Cox regression analysis and receiver operator characteristic (ROC) analysis. All analyses were performed using the Statistical Package for the Social Sciences (SPSS) (version 25, SPSS Company, Chicago, IL). $p<0.05$ was considered statistically significant.

Results

Patient Characteristics

The clinical and postoperative histopathologic information of 101 patients is summarized in Table 1. The median age of all included patients (68 men, 33 women) was 61 years (range, 29–82 years). There were no significant differences

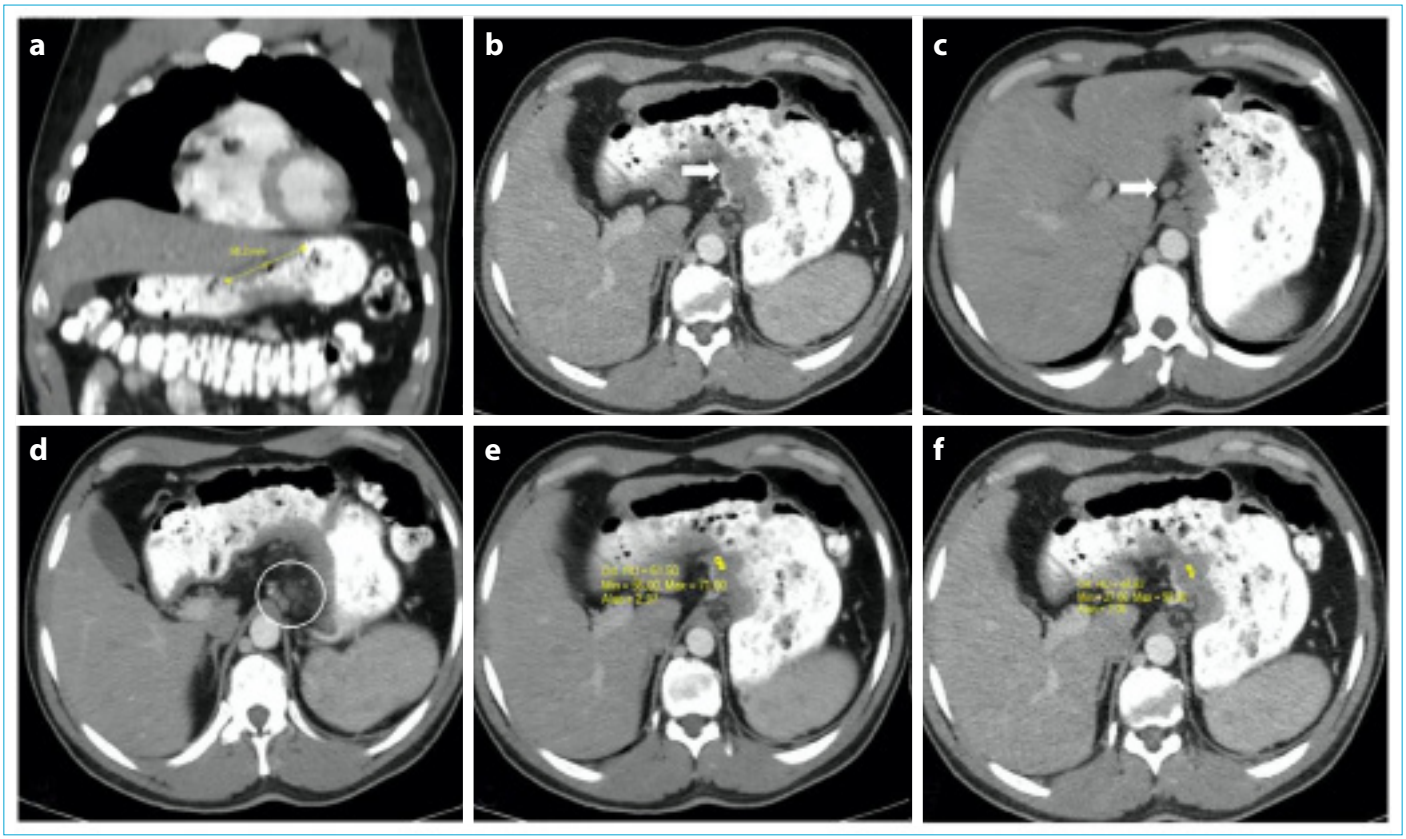

Figure 1. A 41-year-old male patient diagnosed with gastric cancer. Postoperative pathological results: Pathological type: Mucinous cancer, Operation type: Total gastrectomy, Lymph node dissection: D2 dissection, 9 positive (9/25), P T stage: T4, Grade: Grade 2, Lymphovascular invasion: Positive. Preoperative dynamic CT evaluation: **(a)** Longest diameter of tumor: 58 mm **(b)** T stage: T4 due to invasion of vascular (white arrow) **(c** and **d)** N stage (number of pathologic lymph nodes): **4** (white arrow and circle) **(e)** HU in arterial phase: 61 **(f)** HU in venous phase: 48.

Table 1. Characteristics of included 101 patients

Characteristics	Number	%
Sex		
Male	68	32.7
Female	33	67.3
Age (years), median (range)	61 (29–82)	
Pathologic T stage		
pT1	10	9.9
pT2	12	11.9
pT3	24	23.8
pT4	55	54.5
N stage		
N0	14	13.9
N1	24	23.8
N2	21	20.8
N3	41	40.6
Lymphovascular invasion		
Present	91	90.1
Absent	9	8.9
Grade		
Grade 1	42	41.6
Grade 2	32	31.7
Unknown	27	26.7
Lymph node dissection		
D1	17	16.8
D2	82	81.2
Resection status		
R0	85	84.2
R1	16	15.8
Histopathological subtype		
Mucinous	8	7.9
Signet ring cell carcinoma	25	24.8
Intestinal	17	16.8
Diffuse	10	9.9
Medullary	5	5
Adenocancer subtype not specified	36	35.6
Location of tumor		
Cardia	15	14.9
Fundus	2	2
Corpus	14	13.9
Antrum	43	42.6
More than one location	27	26.7
Adjuvant chemotherapy		
Yes	88	87.1
No	13	12.9
Recurrence		
Yes	41	40.6
No	60	59.4
Status of death		
Yes	38	37.6
No	63	62.4
Type of operation		
Subtotal gastrectomy	31	30.7
Total gastrectomy	70	69.3

in age and gender between the OS in univariate and multivariate analysis (p values were 0.22 and 0.72, respectively).

Preoperative CT Findings Compared with OS

The preoperative CT imaging features of included 101 patients are summarized in Table 2. The correlation between CT imaging features including tumor depth, LN status, the longest dimension of tumor, location of the tumor, HU in arterial and venous phases, and OS is summarized in Table 3. Multivariate analysis revealed that none of the preoperative CT features were associated with the OS. However, univariate analysis showed a statistically significant association between CT tumor depth and OS (p<0.001, hazard ratio: 63.5, 95% CI, 48.3–78.8). N stage and longest diameter of tumor on preoperative CT features truly predicted R1 re-

Table 2. Preoperative CT imaging characteristics of included 101 patients

Characteristics	Number	%
CT tumor depth		
T1-T2	22	21.8
T3	45	44.6
T4	34	33.7
LN status		
N0	17	16.8
N1	18	17.8
N2	33	32.7
N3	33	32.7
The longest diameter of tumor		
<3 cm	5	5
3–6 cm	47	46.5
6–9 cm	31	30.7
More than 9 cm	33	32.7
Location of tumor		
Cardia	5	5
Corpus	12	11.9
Minor curvature	5	5
Antrum	49	48.5
More than one location	29	28.7
HU in arterial phase		
<40	33	32.7
40–60	20	19.8
More than 60	47	46.5
HU in venous phase		
<40	13	12.9
40–60	25	24.8
More than 60	62	61.4

CT: Computed tomography; HU: Hounsfield unit; LN: Lymph node.

Table 3. Results of preoperative CT findings compared with OS, univariate, and multivariate survival analyses

Variable	Univariate analysis (p)	Multivariate analysis (p)
CT tumor depth (T1-T2, T3 and T4)	**<0.001 (hazard ratio: 39.3, 95% CI 25.3–53.3)**	**0.11**
LN status (N0, N1, N2, N3)	**0.14**	**0.40**
The longest diameter of tumor (<3 cm, 3–6 cm, 6–9 cm, more than 9 cm)	**0.46**	**0.20**
Location of tumor (cardia, fundus, corpus, greater curvature, minor curvature, antrum, and more than one location)	**0.55**	**0.25**
HU in arterial phase (<40, 40–60, more than 60)	**0.32**	**0.06**
HU in venous phase (<40, 40–60, more than 60)	**0.41**	**0.18**

CT: Computed tomography; HU: Hounsfield unit; LN: Lymph node.

section status (AUC, 0.697; sensitivity, 63%; and specificity, 88%, and AUC, 0.734; sensitivity, 18%; and specificity, 76%, respectively) in ROC analysis (Fig. 2).

Postoperative Pathological Findings Compared with OS

The association between postoperative pathological findings including histopathological subtype, pT1-T4, N stage, grade, lymphovascular invasion, location of the tumor, resection status, type of operation, type of LN dissection, and OS is summarized in Table 4. Multivariate Cox regression analysis showed that the survival ratio after resection was poor for the R1 group and high-grade group than for the R0 and low-grade groups (p=0.001, hazard ratio: 15.8, 95% CI: 3.30–75.9, and p=0.005, hazard ratio: 0.23, 95% CI: 0.085–0.64, respectively). None of the pathological findings except resection status and grade were associated with OS in multivariate Cox regression analysis and univariate analysis.

Recurrence and Prognosis

Thirty-eight of all patients (37.6%) died and 63 (62.3%) were alive. The mean survival time was calculated as 39.3 months, ranging between 25.3 and 53.3±7.1 months (Fig. 3). Forty patients had recurrences during follow-up and 61 patients had no recurrences. The survival rate was worse for recurrent patients than non-recurrent patients (p<0.001).

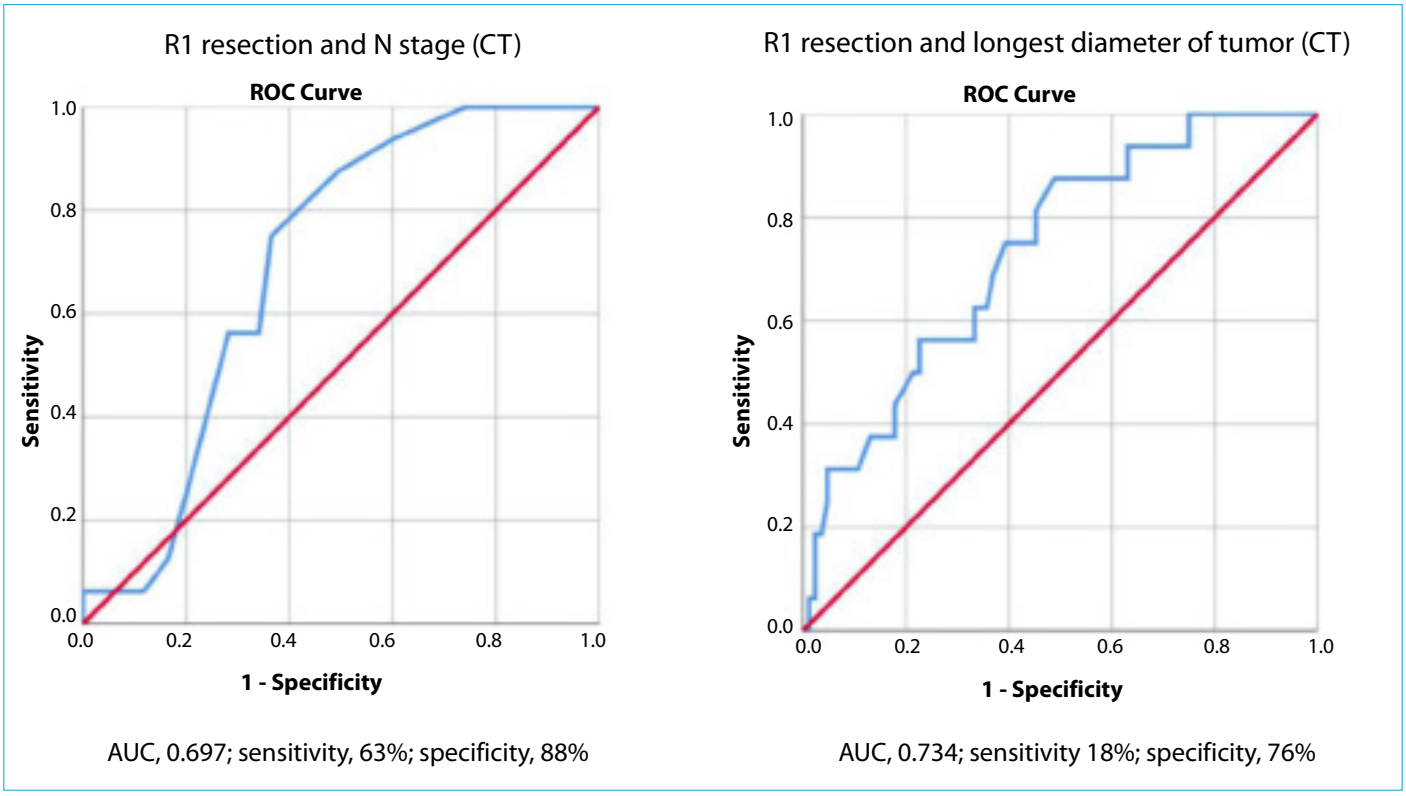

Figure 2. The ROC analysis of N stage and longest diameter of tumor and R1 resection.

Table 4. Results of clinical and postoperative pathological findings compared with OS, univariate, and multivariate survival analyses

Variable	Univariate analysis (p)	Multivariate analysis (p)
Age	**0.31**	**0.22**
Gender	**0.92**	**0.72**
Histopathological subtype (tubular, papillary, tubulopapillary, mucinous, signet ring cell carcinoma, intestinal, diffuse, adenosquamous, adenocancer subtype not specified)	**0.58**	**0.65**
Resection status (R0, R1)	**<0.001**	**<0.001 (hazard ratio: 15.8, 95% CI 3.30–75.9)**
Pathologic T stage (pT1-T4)	**0.004**	
N stage (N0, N1, N2, N3)	**0.001**	**0.63**
Grade (grade 1-3)	**0.009**	**0.005 (hazard ratio: 0.23, 95% CI 0.085-0.64)**
Lymphovascular invasion	**0.095**	**0.98**
Location of tumor (cardia, fundus, corpus, great curvature, small curvature, antrum)	**0.65**	**0.77**
Type of operation (total, subtotal gastrectomy)	**0.42**	**0.55**
Type of lymph node dissection (D1, D2)	**0.87**	**0.92**
Recurrence (Yes, no)	**<0.001**	**<0.001 (hazard ratio: 63.5, 95% CI 48.3-78.8)**
Adjuvant chemotherapy (Yes, no)	**0.43**	**0.10**

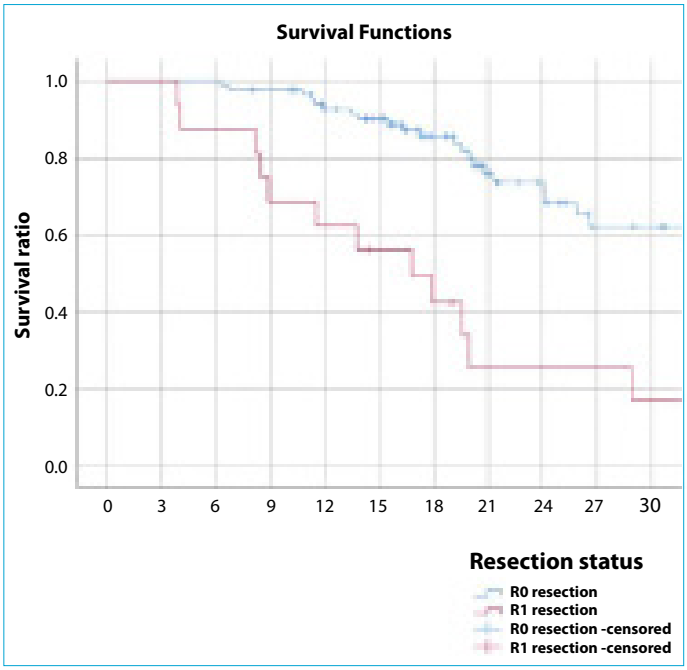

Figure 3. Overall survival curve of a patient according to the resection status.

Discussion

In the present study, we evaluated the use of preoperative CT characteristics of GC for predicting OS. None of the preoperative CT features were correlated with OS in multivariate analysis. Nevertheless, N stage and the longest dimension of the tumor on CT scans truly estimated R1 resection status (AUC, 0.697; sensitivity, 63%; and specificity, 88%, and AUC, 0.734; sensitivity, 18%; and specificity, 76%, respectively), which is one of the postoperative pathological findings correlated with OS. As neoadjuvant chemotherapy has played an important role in GC management, accurate prognostic evaluation has been essential for choosing the correct treatment. GC can have large variations in clinical outcomes even among patients with the same stage.[6,18,19] Many studies in the literature evaluated the relationship between CT tumor depth and prognosis. Park et al.[20] published a large-scale retrospective study in 2010 and showed that CT tumor depth was a significant prognostic factor for OS in curative resected GC patients. In our study, CT tumor depth was correlated with OS in univariate analysis but not multivariate analysis. They categorized four groups as follows: T1, tumor invasion of mucosa and submucosa; T2, tumor invasion of muscularis propria or subserosa; T3, tumor invasion of serosa; and T4, tumor invasion of adjacent structures. However, CT is not the ideal radiological method for staging T classification, especially in T1 and T2 tumors due to insufficient differentiation between submucosa and muscularis propria. In our study, we categorized T1 and T2 in the same group. Another difference was the number of patients in subgroups, namely in their study, the T1 and T2 groups constituted 74.5% of the patients, but in our study, this rate was 21.8%. In another recent study, T2, T3, and T4 tumors were separately evaluated, and additionally, unlike our study, T4 tumor was divided into three groups as follows: minimal extramural (<1 mm), spiculated extramural, and nodular extramural.[11] They showed that specular and nodular extramural tumor infiltrations were independent

predictive factors of recurrent disease and lower DFS. They did not find differences between T2, T3, and T4 groups in survival similar to our study. Therefore, there is no consensus on this issue in the literature due to differently designed studies.

The pathologic N stage is one of the most dependable prognostic indicators for patients diagnosed with operable GC.[21,22] Correct evaluation of the preoperative N stage with CT in GC is insufficient because of lower sensitivity in <pN2 and micrometastatic groups.[11] In our study, the LNs with a short-axis diameter greater 8 mm were round in shape and had a central hypodensity secondary to the necrosis or settled in a cluster (three nodes or more), which were considered to be metastatic similar to previous studies.[11,17] Ohashi et al.[17] investigated preoperative N staging accuracy using CT and showed low sensitivity with an overall accuracy of 46.3%. Differently, Park et al.[11] evaluated the correlation between DFS and LN status and showed an important correlation with DFS on univariate analysis but not multivariate analysis. They categorized LN status into two categories (N0-N1 and N2-N3). Our study did not find a correlation with the OS in all four groups (N1, N2, N3, and N4) by univariate and multivariate analysis. As mentioned in the previous paragraph, a large-scale retrospective study showed that clinical N stage was a significant prognostic factor for OS in multivariate analysis.[20] However, when we look at the number of patients in the N stage subgroups in their study, we see that the N2 and N3 subgroups are only 0.1% in total. This rate was 61.4% in our study. Another critical point is that none of these studies and our study were not matched the LNs node by node with CT findings and pathological findings. Future studies may be necessary to evaluate the radiologic LN evaluation criteria by assessing short diameter and morphological features and functional imaging modalities.

Tumor size is a poor prognostic factor in many studies published in this area so far.[11,17,20,23] For example, tumors of 5–10 cm on preoperative CT imaging had a significantly worse prognosis than <5 cm tumors in one study.[11] However, no statistically significant correlation was found between the tumor larger than >10 cm and DFS in the same study. Another study compared pathologic tumor size and OS and showed >4.5 cm tumors had lower OS in resectable GC patients. Another study included only T1-T2 and N0 patients and found that tumor size was correlated with recurrent disease in early GC.[23] We categorized the longest diameter on the axial, coronal, or sagittal plane into four groups (<3 cm, 3–6 cm, 6–9 cm, and more than 9 cm). We did not find statistically significant differences between groups in OS. We think that the reasons for these differences were the inclusion of patients at different stages in studies, the utilization of neoadjuvant chemotherapy in some patients, and the different number of patients in subgroups.

Tumor angiogenesis and intratumoral vascularity are significant factors in GC patients' prognosis in many studies.[24-26] Although being an old research area, the number of studies investigating the correlation between tumor enhancement on dynamic CT and OS is relatively low.[13,27] Most of the studies have investigated the value of enhancement in differentiating benign from malignant lesions, evaluating tumor, node, and metastasis, staging, determining anticancer therapy's efficacy, and discriminating the pathologic types.[28-30] Komori et al.[13] reported that measuring the extent of arterial tumor enhancement by placing the ROI at the inner tumor margin could be an independent prognostic factor for operated GC patients. They measured the ratio between the normal gastric wall and tumor wall enhancement in the arterial dynamic phase of CT imaging different from our study. We measured HUs in arterial and venous phases separately and found no statistically significant correlation with the OS (p=0.06). Their study[13] population was lower than our study population (41 and 101, respectively), although it was relatively homogeneous distribution of patients in subgroups. Another study showed better prognosis and OS in the low-enhancement group than the high-enhancement group.[27] They measured enhancement in arterial, venous, and delayed venous phases, and a statistically significant correlation between OS was found in only the delayed phase. Similar to our study, no correlation was found in arterial and venous phases. This area will be replaced by texture analysis and radiomic studies.

According to our results, the survival rate after resection was worse for the R1 group than for the R0 group, as expected. N stage and the longest dimension of the tumor on CT scans truly predicted R1 resection status (AUC, 0.697; sensitivity, 63%; and specificity, 88%, and AUC, 0.734; sensitivity, 18%; and specificity, 76%, respectively). These results are partially consistent with the literature. A large-scale study showed that if patients had high clinical T classification or N classification, the curative R0 resection rate decreased significantly.[20]

This study has some limitations. First, this is a retrospective and single-center study. Second, preoperative T staging of the tumor was evaluated only by CT imaging, although EUS could contribute additional value for distinguishing the layer of the gastric wall. Third, we did not add the unenhanced scans in dynamic preoperative CT imaging protocol, leading to a more accurate enhancement measurement.

Conclusion

Accurate preoperative evaluation of GC is essential for treatment planning and prognosis prediction, especially in increasing neoadjuvant therapies in preoperative settings. CT is the most used modality for preoperative evaluation, but none of the preoperative CT findings were correlated with the OS, according to our results. However, CT features, including the longest dimension of the lesion and the number of pathological LNs, can predict R1 resection, which is an independent factor for a worse prognosis.

Disclosures

Ethics Committee Approval: The study was approved by the Ethics Committee of Istanbul University Oncology Institute (No: 109412, dated 02.07.2020).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – I.K.Y., S.M.E., I.D.; Design – I.K.Y., I.D., S.V.; Supervision – S.V., S.M.E.; Materials – I.K.Y., I.D.; Data collection &/or processing – I.K.Y., I.D., S.M.E.; Analysis and/or interpretation – I.K.Y., I.D.; Literature search – I.K.Y., S.V.; Writing – I.K.Y., S.M.E.; Critical review – S.M.E., S.V.

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