Int J Clin Exp Med 2015;8(8):12801-12809
www.ijcem.com /ISSN:1940-5901/IJCEM0012074

*Original Article*

# Survival implications of pretreatment pelvic CT in rectal cancer patients after neoadjuvant chemoradiotherapy and surgery

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Received June 29, 2015; Accepted August 11, 2015; Epub August 15, 2015; Published August 30, 2015

**Abstract:** Purpose:To determine the correlation between pretreatment computed tomography (CT) data and survival duration after neoadjuvant chemoradiotherapy and surgery for locally advanced rectal cancer. Materials and methods: 122 consecutive patients with advanced rectal cancer were assessed retrospectively. Pretreatment imaging and postoperative data were evaluated through Kaplan-Meier and Cox proportional hazard regression analyses. Results: Pretreatment CT identified 557 metastatic lymph nodes (mean, 4.55 per patient; median 4). Survival durations were measured during the period between the application of CT and death or the last follow-up examination. Univariate analysis showed that the following factors had a significant impact on survival: maximum tumor diameter ($P$ = 0.019), distance from inferior tumor margin to anorectal ring ($P$ <0.0001), number of lymph nodes involved in patients with short-axis, lymph node diameter ≥8 mm ($P$ <0.0001) in pretreatment CT, distance from the anorectal ring ($P$ = 0.027), ypN stage ($P$ = 0.0008), ypM stage ($P$ = 0.046) and number of metastatic lymph nodes ($P$ <0.0001) in clinical assessment. Multivariate analysis showed that the following factors were significant: number of lymph nodes in patients with short-axis lymph node diameter ≥5 mm but <8 mm ($P$ = 0.044) and in those with this diameter ≥8 mm ($P$ = 0.028; pretreatment CT) and number of metastatic lymph nodes (assessed in histopathological examination). Conclusion: Pretreatment lymph node size and number can predict survival duration after treatment for locally advanced rectal cancer. For patients with lymph nodes >8 mm (short-axis diameter) and/or >1, such lymph nodes tend to have a poor performance for prognosis.

**Keywords:** Locally advanced rectal cancer, multislice spiral CT, lymph node size, survival

## Introduction

Rectal cancer has been a major cause of cancer mortality in the world. Fortunately, treatment outcomes for rectal cancer have dramatically improved since the application of total mesorectal excision (TME) [1]. For locally advanced (transmural and/or node-positive) rectal cancer, neoadjuvant therapy followed by TME is considered to be a standard treatment [2, 3]. Due to inadequate single-modality therapy for locally advanced stages, clinical staging is very important for appropriate treatment selection in order to avoid poor clinical outcomes. Prognostic indicators of poor survival have been identified in histopathology studies on rectal cancer. Among these factors, the characteristics of lymph node metastasis are the most important in estimating patient outcomes after surgery [4-6]. However, accurate postoperative histopathological staging to predict survival cannot be performed to all the patients. For example, accurate N staging is not available for patients with less than 15 lymph nodes removed [7]. Besides, during intensive multimodality treatment of rectal cancer [8], the postoperative characteristics of the lymph nodes often change after neoadjuvant radiotherapy or chemotherapy. In addition, histopathological diagnosis, which is obtained post-

operatively, is not suitable for determining lymph node status after neoadjuvant radiotherapy or chemotherapy.

Therefore, the application of imaging modalities for pretreatment assessment and prognosis is recommended. Non-invasive imaging modalities such as endoluminal ultrasonography (US), computed tomography (CT) and magnetic resonance imaging (MRI) are effective diagnostic tools for assessments of lymph node involvement and staging of rectal cancer. A meta-analysis showed that lymph node involvement estimates determined by US, CT, and MRI are comparable to one another [9]. In recent years, positron emission tomography (PET) has substantially changed oncological practice. Neverthelsee, it does not contribute much to the visualization of mesorectal lymph nodes. In contrast, recent advances in CT such as multidetector spiral CT and CT cine viewing have allowed for the detection of small lymph nodes which were previously undetectable in CT [10]. Although the effectiveness of CT in the assessment of lymph node involvement in rectal cancer has been widely recognized [10-13], its value for predicting patient survival has scarcely been evaluated.

In the retrospective study, the correlation of pretreatment CT data and clinical data with survival of patients with locally advanced rectal cancer was assessed, and in particular, the survival impact of lymph node size measured with pretreatment pelvic CT determined, provided that pretreatment CT images of lymph nodes can reflect the biological behavior of the tumor and may be important for prognosis.

## Patients and methods

### *Patients*

This study is approved by the institutional ethics committee. The study group consists of a consecutive series of 122 patients with newly diagnosed advanced rectal cancer between January 2003 and January 2010, including 90 men and 32 women with a mean age of 55 years (range, 24-80 years). The inclusion criteria are as follows: (a) biopsy-proven rectal adenocarcinoma of clinical stages II or III (as per American Joint Committee on Cancer, AJCC, edition seven), (b) absence of any preoperative treatment before CT examination, (c) absence of other concurrent malignant or inflammatory diseases of any pelvic organ, (d) administration of neoadjuvant therapy prior to surgery, and (e) availability of follow-up data, including clinical and treatment information in the medical records.

All patients undergone plain CT (Brilliance 16, PhilipsMedical Systems; 5-mm slices through the pelvis, from the iliac crests to the anal verge) together with intravenous contrast-enhanced CT (Iopamiro solution, 350 mg I/ml, Bracco, Milano, Italy or Iopromide injection, Ultravist, 370 mg I/ml, Schering, Erlangen, Germany), approximately 80~100 ml of non-ionic iodinated contrast was administered intravenously at 3~4 ml/s.

Besides, they were all treated with preoperative radiation (45-50.4 Gy) with or without concurrent chemotherapy (cisplatin [PDD] plus fluorouracil [5-FU], 5-FU alone or 5-FU plus calcium folinate (CF); 5-FU dose, 350 mg/m$^2$/day bolus or 225-300 mg/m$^2$/day continuous intravenous injection). The surgeries were performed 6-8 weeks after the completions of preoperative chemoradiotherapies.

The means of postoperative monitoring included outpatient visits, telephone interviews and information obtained from death certificates. Only patients who died of rectal cancer were considered in the evaluation of tumor-related deaths. Survival durations were measured during the period between theapplication of pretreatment CT examination and the time of death or the last follow-up date. Follow-ups were conducted until February 2012.

### *CT parameters*

All images were retrieved from a PACS (Picture Archive and Communication System) or DICOM (Digital Imaging and Communications in Medicine) server and reviewed by two radiologists (Cui CY and Li L with 8 and 15 years of experience, respectively) who were working together in a workstation. Disagreements on the evaluations were resolved by consensus. The following parameters from the pretreatment CT images were utilized for survival analysis: tumor length, maximum tumor diameter (measured on axial images), depth of invasion of rectal wall, distance between tumor rim and mesorectal fascia (D), distance from the inferior margin of the tumor to the anorectal ring (L), total number of lymph nodes affected and the maximum diameter of the lymph nodes on the short axis (d).

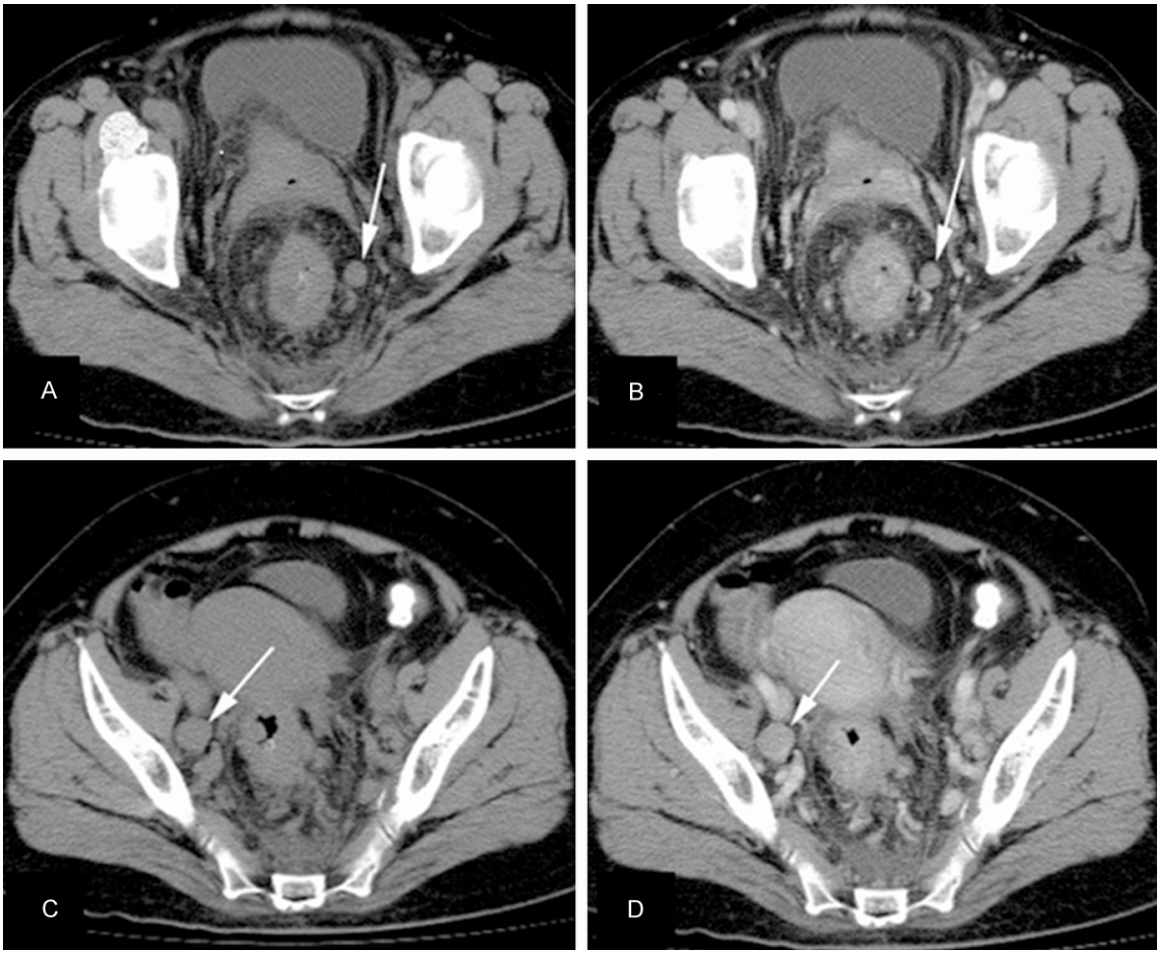


**Figure 1.** Computed tomography scans of regional lymph nodes (A, B: Arrows) and lymph nodes near the right iliac vessels (C, D: Arrows) showing metastases from rectal cancer.

For lymph node analyses, patients were divided into four groups according to lymph node size, as assessed by using CT data: Group ①, d <3 mm; Group ②, 3 mm ≤d <5 mm; Group ③, 5 mm ≤d <8 mm; and Group ④, d ≥8 mm. Patients were also grouped according to whether their "d" values were more or less than a given cutoff. 3, 5 and 8 mm were selected as cutoff values for lymph node size, and obtained Groups A1, A2; B1, B2; and C1, C2 were chosen. The Group A1 has d <3 mm, Group A2 d ≥3 mm; Group B1 d <5 mm, Group B2 d ≥5 mm; Group C1 d <8 mm and Group C2 d ≥8 mm [14, 15].

*Clinical parameters*

The following postoperative clinical parameters were assessed: distance between the most inferior aspect of the primary tumor and the anorectal ring as assessed by using digital rectal examination or endoscopy, maximum tumor diameter (mm), depth of invasion of the rectal wall, number of metastatic lymph nodes, Dukes stage and ypTNM (yielding pathologic Tumor Node Metastasis) stage (as per the AJCC TNM classification, 2009).

*Statistical analysis*

The Statistical Package was adopted for the Social Sciences program, version 16.0 (SPSS, Chicago, IL, USA) and for all calculations. The incidences of lymph nodes metastasis in patients using histopathological examination and lymph node status assessed using pretreatment CT were compared and analyzed using the $x^2$ test.

Univariate analysis was performed with the Kaplan-Meier method, and potential prognostic factors were tested for univariate statistical sig-

**Table 1.** Lymph node status assessed using pretreatment computed tomography (CT) and histopathological examination

| Number | All four groups of Test LN | CT parameters | | | | Postoperative parameters | |
|---|---|---|---|---|---|---|---|
| | | Group ① LN | Group ② LN | Group ③ LN | Group ④ LN | Test LN | LNM |
| Median number of LN | 4 | 1 | 0 | 1 | 1 | 6 | 0 |
| Max number of LN | 16 | 8 | 7 | 8 | 4 | 37 | 15 |
| Range of LN per patient | 0~16 | 0~8 | 0~7 | 0~8 | 0~4 | 0~37 | 0~15 |
| Total of LN | 557 | 173 | 115 | 227 | 42 | 864 | 104 |

Footnote: LN: lymph node; LNM: lymph node metastasis.

**Table 2.** Univariate analysis of pretreatment computed tomography (CT) and clinical parameters

| Factors | *P*-value |
|---|---|
| Pretreatment CT parameters | |
| Maximum tumor thickness | $P = 0.019$ |
| Maximum tumor diameter | P = 0.181 |
| Depth of invasion of rectal wall | $P = 0.913$ |
| Distance between tumor rim and mesorectal fascia (D) | $P = 0.991$ |
| Distance between inferior tumor margin and anorectal ring (L) | $P < 0.0001$ |
| Number of lymph nodes | $P = 0.282$ |
| Number of lymph nodes in Group ① | $P = 0.282$ |
| Number of lymph nodes in Group ② | $P = 0.911$ |
| Number of lymph nodes in Group ③ | $P = 0.276$ |
| Number of lymph nodes in Group ④ | $P < 0.0001$ |
| Clinical parameters | |
| Distance between inferior tumor margin and anorectal ring | $P = 0.027$ |
| Maximum tumor diameter | $P = 0.254$ |
| Depth of invasion of rectal wall | $P = 0.190$ |
| Dukes stage | $P = 0.311$ |
| ypT | $P = 0.799$ |
| ypN | $P = 0.0008$ |
| ypM | $P = 0.046$ |
| LNM | $P < 0.0001$ |

Footnote: ypT: yielding pathologic Tumor; ypN: yielding pathologic Node; ypM: yielding pathologic Metastasis; LNM: lymph node metastasis.

nificance through the log-rank test. All the parameters mentioned above were tested as prognostic factors. A two-sided *P*-value of 0.05 or less was considered to indicate statistical significance. Significant factors were entered in a multivariate analysis using Cox proportional hazard regression analysis; $P < 0.05$ was considered to denote a significant difference.

For lymph node analyses, univariate analysis and survival curves were calculated with the Kaplan-Meier method.

## Results

According to the review of all the pretreatment CT images of the 122 patients, a total of 557 lymph nodes, or 0-16 lymph nodes per patient (mean, 4.55 per patient; median, 4; **Figure 1**), were affected. However, no lymph node was affected in two patients synchronously. In addition, 173, 115, 42 and 227 lymph nodes were affected in Groups ①, ②, ③ and ④, respectively (**Table 1**). A higher incidence of metastatic LNs was found when d <3 mm; 3 mm ≤d <5 mm; 5 mm ≤d <8 mm on CT was present than in patients using histopathological examination lymph node metastasis, respectively (31.28% versus 12.04%, $x^2 = 79.423$, $P = 0.001$; 20.79% versus 12.04%, $x^2 = 19.796$, $P = 0.001$; 41.05% versus 12.04%, $x^2 = 85.105$, $P = 0.001$). The incidence of metastatic LNs in patients with group d ≥8 mm on CT was lower than in patients using histopathological examination lymph node metastasis (7.59% versus 12.04%, $x^2 = 7.199$, $P = 0.007$).

*Survival analysis*

By February 2012, the duration of follow-up had ranged from 38 to 92 months, and the median survival time of the patients was 48

**Table 3.** Multivariate analysis of pretreatment computed tomography (CT) and clinical parameters

| Variable | B | HR | 95% CI | *P** |
|---|---|---|---|---|
| Pretreatment CT parameters | | | | |
| Tumor length | 0.073 | 1.076 | (0.954, 1.213) | 0.234 |
| Maximum tumor diameter | 0.012 | 1.012 | (0.974, 1.052) | 0.546 |
| Depth of invasion of rectal wall | -0.613 | 0.541 | (0.063, 4.627) | 0.575 |
| Distance between tumor rim and mesorectal fascia (D) | 0.019 | 1.019 | (0.863, 1.203) | 0.822 |
| Distance between inferior tumor margin and anorectal ring (L) | -0.093 | 0.911 | (0.827, 1.004) | 0.060 |
| Number of lymph nodes | 0.731 | 2.076 | (0.849, 5.078) | 0.109 |
| Number of lymph nodes in Group ① | -0.047 | 0.954 | (0.422, 2.157) | 0.911 |
| Number of lymph nodes in Group ② | -0.509 | 0.601 | (0.242, 1.493) | 0.273 |
| Number of lymph nodes in Group ③ | -1.196 | 0.302 | (0.094, 0.970) | 0.044 |
| Number of lymph nodes in Group ④ | 1.046 | 2.845 | (1.118, 7.243) | 0.028 |
| Clinical parameters | | | | |
| Distance between inferior tumor margin and anorectal ring | 0.247 | 1.280 | (0.912, 1.797) | 0.153 |
| Maximum tumor diameter | -0.120 | 0.887 | (0.615, 1.281) | 0.523 |
| LNM | 0.374 | 1.454 | (1.114, 1.898) | 0.006 |
| Dukes stages | -0.316 | 0.729 | (0.501, 1.061) | 0.099 |
| ypT | 0.669 | 1.953 | (0.984, 3.879) | 0.056 |
| ypN | 0.030 | 1.030 | (0.330, 3.214) | 0.959 |
| ypM | 0.259 | 1.296 | (0.167, 10.558) | 0.804 |

Footnote: B, meaning the regression coefficient; HR, Hazard ratio; CI, Confidence interval; LNM: lymph node metastasis; ypT: yielding pathologic Tumor; ypN: yielding pathologic Node; ypM: yielding pathologic Metastasis. **P* value were calculated using an adjusted Cox proportional-hazards model.

**Table 4.** Univariate survival analysis of lymph node size, specifically, maximum diameter in the short axis, as measured on computed tomography

| Cutoff value (mm) | Variable (mm) | No. of patients | Mean survival (months) | *P*-value |
|---|---|---|---|---|
| 3 | <3 (A1) | 18 | 55.88 | 0.573 |
| | ≥3 (A2) | 104 | 51.91 | |
| 5 | <5 (B1) | 21 | 57.15 | 0.343 |
| | ≥5 (B2) | 101 | 51.37 | |
| 8 | <8 (C1) | 95 | 59.42 | 0.000 |
| | ≥8 (C2) | 27 | 33.49 | |

Footnote: Group A1 has diameter <3 mm, Group A2 d diameter ≥3 mm; Group B1 d diameter <5 mm, Group B2 d diameter ≥5 mm; Group C1 d diameter <8 mm and Group C2 d diameter ≥8 mm.

months. Among these 122 patients, 23 died of their tumors.

*Prognostic implications of pretreatment factors*

Univariate analysis (**Table 2**) has revealed that the following pretreatment CT parameters have a significant impact on patient outcome: maximum tumor diameter ($P = 0.019$), L ($P < 0.0001$) and number of lymph nodes affected in Group ④, d ≥8 mm ($P < 0.0001$). Among clinical parameters, distance from the anorectal ring ($P = 0.027$), ypN stage ($P = 0.0008$), ypM stage ($P = 0.046$) and number of metastatic lymph nodes ($P < 0.0001$) have a significant impact on survival. The other pretreatment CT and clinical parameters do not have prognostic significance.

Multivariate analysis (**Table 3**) showed that only the following variables were independent factors for patient outcome: number of lymph nodes affected (in pretreatment CT) in Groups ③, 5 mm ≤d <8 mm ($P = 0.044$) and ④, d ≥8 mm ($P = 0.028$) and number of metastatic lymph nodes (in histopathological assessment).

The results of multivariate Cox proportional hazards model have confirmed that the number of lymph nodes affected as determined on pretreatment CT scans, is an important prognostic factor (**Table 3**). Besides, the relationship between survival time and different cutoff values for lymph node size, as determined by pre-

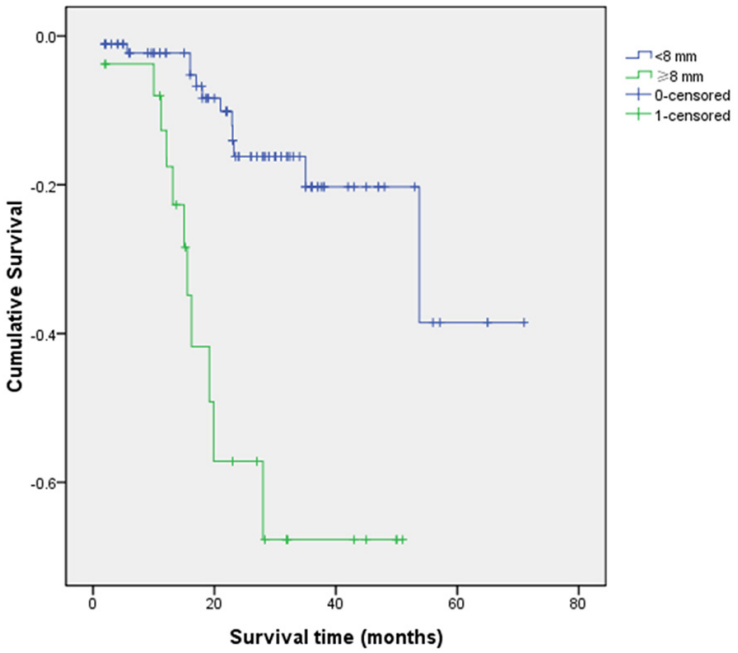


**Figure 2.** Overall survival was significantly greater in patients with maximum short-axis lymph node diameter <8 mm, as measured on pretreatment computed tomography, than in patients with this diameter ≥8 mm (*P* <0.001).

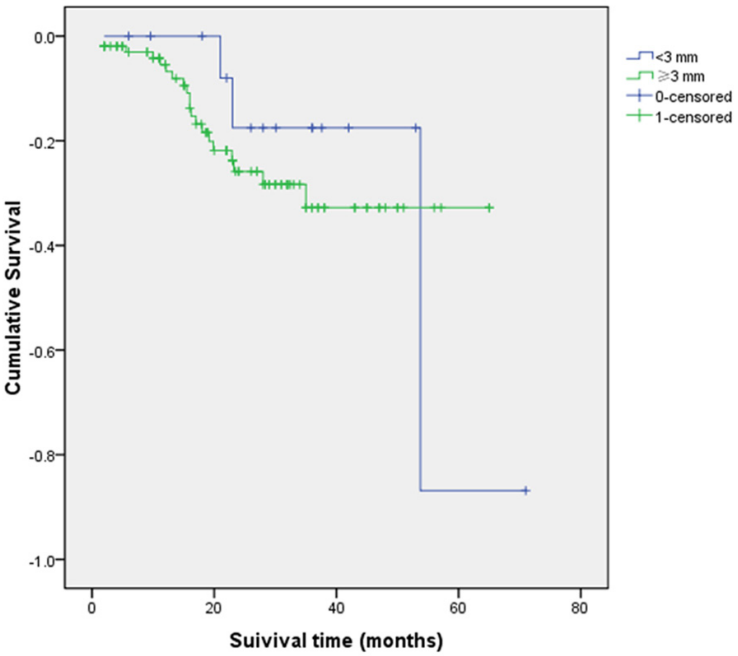


**Figure 3.** No significant difference in overall survival was observed between patients with maximum short-axis lymph node diameter <3 mm, as measured on pretreatment computed tomography, and patients with this diameter ≥3 mm (*P* = 0.573).

treatment CT, has also been ascertained. Compared with the patients with the maximum lymph node diameter on the short axis ≥8 mm, the mean survival time of those with the maximum lymph node diameter on the short axis <8 mm is significantly longer. (59.4 months vs. 33.5 months, *P* <0.001; **Table 4**; **Figure 2**).

Furthermore, there is no such correlation between survival time and lymph node size observed when diameters of 3 mm and 5 mm were chosen as the cutoffs (**Figures 3** and **4**).

## Discussion

Many prognostic factors for rectal cancer have been assessed, such as tumor markers (serum carcinoembryonic antigen and serum carbohydrate antigen-199), different operation methods and histopathological factors (intramural depth, presence of regional nodal metastasis, degree of differentiation) [16-18]. However, these risk factors are not always helpful in guiding treatments, because some of them can be determined only after operation. For example, histopathological factors cannot be utilized to determine whether preoperative radio- or chemotherapy should be administered or not. Among the above factors, only serum concentrations of tumor markers can be utilized as pretreatment prognostic factors. Besides, although the importance of prognostic factors for the individualization of the treatment approach to rectal cancer has been reported in many studies, no definitive prognostic predictors of treatment response have been identified [19]. Therefore, whether CT, a non-invasive and widely used tool, can be utilized to predict the survival duration of rectal cancer patients or not is assessed.

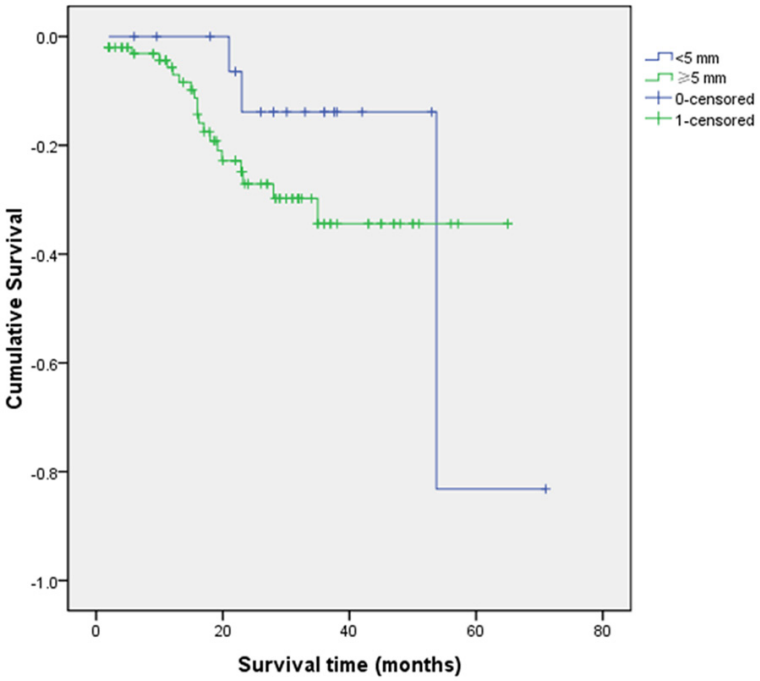


**Figure 4.** No significant difference in overall survival was observed between patients with maximum short-axis lymph node diameter <5 mm, as measured on pretreatment computed tomography, and patients with this diameter ≥5 mm ($P$ = 0.343).

In addition, Transrectal US (TRUS) and MRI are also utilized to diagnose and stage rectal cancer; however, neither has been proven to be superior to pelvic CT for predicting lymph node status. Although TRUS is widely available and can perform T staging with high accuracy, its accuracy for N staging is questionable [20]. Similarly, although MRI is a promising staging modality, its high cost restricts its widespread use, and its superiority to CT for N staging has yet to be demonstrated. As a result, pelvic CT is probably the most commonly used imaging modality for the staging of rectal cancer.

The treatment for rectal cancer depends on the cancer stage. Surgery alone is adequate for rectal cancer at Stage I, whereas preoperative chemoradiotherapy seems to be the best approach for rectal cancer at Stage II-III. Most clinical trials on preoperative chemoradiotherapy have been performed on patients clinically staged as T3-4 and/or node-positive patients [21, 22]. Therefore these patients were selected for the study.

The effectiveness of CT for assessing lymph node involvement in rectal cancer is widely acknowledged [10, 12, 13]. However, its value for predicting patient survival has not been evaluated. In this retrospective study, the elucidation of the prognostic implications of lymph node size, as assessed by using pretreatment pelvic CT, is attempted, for patients with locally advanced rectal cancer.

It is found that both the size and number of lymph nodes affected are survival factors for locally advanced rectal cancer. Univariate, survival curve and multivariate analyses showed that patients with maximum lymph node diameter on the short axis ≥8 mm and patients with a higher number of such lymph nodes tend to have a worse prognosis. In the cases of lymph nodes with short-axis diameter ≥5 mm and <8 mm (**Table 2**), no significant impact of the number of lymph nodes affected was found on survival duration (**Figure 4**). However, multivariate Cox proportional hazards model showed a significant impact (**Table 3**).

The possible reasons for these conflicting results are insufficient sample size, measurement error and number of lymph nodes affected in Group ③ (5 mm ≤d <8 mm). Different results might be obtained, if different cutoff values such as, 5-6 mm, 6-7 mm and 7-8 mm are chosen. Therefore, it is believed that a similar study should be performed with MRI, which has a higher image resolution than CT.

## Conclusion

This study showed that both the number and size of lymph nodes are useful predictors for the survival of patients with locally advanced rectal cancer treated with neoadjuvant therapy followed by surgery. Patients with lymph nodes with maximum diameter on the short axis ≥8 mm, as assessed on pretreatment CT scans, are more likely to have a worse prognosis. As a result, these CT criteria are helpful in planning appropriate multimodality treatment.

## Acknowledgements

This work was funded by grants from the National Nature Science Foundation of China (NSFC) (No. 81271622, 81471711), the Guangdong Province of Higher School "Thousand Hundred Ten Talents Project" (No. 84000-52010004), the Nature Science Foundation of Guangdong Province, China (No. 2014A030311036) and the Science and Technology Planning Project of Guangdong Province, China (No. 2013B021800161).

## Disclosure of conflict of interest

None.

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