HHS Public Access

Author manuscript

J Surg Oncol. Author manuscript; available in PMC 2020 November 01.

Published in final edited form as:

J Surg Oncol. 2019 November ; 120(6): 932–939. doi:10.1002/jso.25679.

A novel preoperative risk score to predict lymph node positivity for rectal neuroendocrine tumors: An NCDB analysis to guide operative technique

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Abstract

Background/Objective: Staging and type of resection for rectal neuroendocrine tumors (R-NETS) relies on preoperative identification of lymph node (LN) involvement. Study objective was to develop a Preoperative Rectal Stratification Score (PReSS) for LN-positivity and to assess the association of PReSS with overall survival (OS).

Methods: All patients in the National Cancer Database (2004–2014) with non-metastatic/nonfunctional R-NETS were included. Tumor size was divided into three categories (<1, 1–2, and ≥2 cm).

Results: Among 383 patients, median age was 57 years, 52% were male (n = 200), median tumor size was 1.4 cm, 43% had positive LNs (n = 163). On univariate analysis, age > 60, poorly differentiated grade, depth of invasion past submucosa, and size >1 cm were associated with LN positivity. On multivariable analysis, depth of invasion past submucosa, and increasing tumor size >1 cm remained associated with LN positivity. As these can be determined preoperatively, incidence of LN positivity was determined for each combination of tumor size and depth of invasion. Each variable was assigned a score to create a PReSS of four groups (0–3) associated with an increasing rate of LN-positivity (PReSS group 0: 11%, 1: 38%, 2: 50%, 3: 78%, $P < .01$). PReSS correlated with 10-year OS (PReSS 0: 90%; 1: 81%; 2: 59%; 3: 41%).

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MEETING PRESENTATION

This manuscript was presented at the 2019 American Society of Colon and Rectal Surgeons annual meeting in Cleveland, OH.

DATA ACCESSIBILITY

The data that support the findings of this study are available from the National Cancer Database. Restrictions apply to the availability of these data, which were used under license for this study. Data are available authors with the permission of the National Cancer Database.

Conclusion: For R-NETS, depth of invasion and tumor size predict LN positivity and both can be obtained preoperatively. PReSS incorporates both variables and stratifies tumors into four risk groups of progressively increasing LN positivity and should be used to guide surgical approach.

Keywords

endoscopic resection; endoscopic ultrasound; low anterior resection; lymph node metastasis; rectal neuroendocrine tumor

1 | INTRODUCTION

The biologic behavior of neuroendocrine tumors and their associated outcomes vary widely based on the anatomic location of the primary tumor. As a result, guidelines regarding management are site-specific. For rectal neuroendocrine tumors, resection is routinely recommended for all tumors, but the type of resection depends predominantly on tumor size given its previously established concordance with lymph node status which has historically been shown to predict worse tumor biology.[1–5] Consequently, successful staging and selection for type of resection for rectal neuroendocrine tumors relies on preoperative identification of lymph node involvement. However, accurate preoperative evaluation of lymph node status remains difficult in clinical practice.

Multiple modalities are currently available for the preoperative evaluation and staging of rectal tumors.[6] Endorectal ultrasound (ERUS) is the most commonly used modality, and its accuracy for assessing depth of invasion ranges from 75% to 90%.[7–10] In regard to nodal status, the accuracy of ERUS is equally variable ranging from 75% to 88% due to its potential inability to assess involved nodes that may exist higher or deeper in the mesorectum. Similarly, magnetic resonance imaging (MRI) has demonstrated accuracy rates of up to 80% for depth of invasion, but only approximately 60% for nodal status.[11,12] Due to this potential low accuracy in assessing nodal status, and in the absence of other specific biomarkers, clinicians and expert consensus guidelines routinely rely on tumor size for recommendations regarding operative management.

Indeed, current guidelines from the National Comprehensive Cancer Network (NCCN) recommend endoscopic resection of tumors smaller than 1 cm and radical resection with a low anterior resection or an abdominoperineal resection for tumors larger than 2 cm. For tumors 1 to 2 cm in size, controversy remains regarding their optimal management and current guidelines recommend preoperative staging with ERUS or MRI to assess for the depth of invasion and evaluate candidacy for an endoscopic versus formal, anatomic resection.[13] The European Neuroendocrine Tumor Society and The North American Neuroendocrine Tumor Society propose similar size-based guidelines.[14,15]

Given the potential morbidity and long-term effects on quality of life associated with a formal resection of a rectal tumor, accurately predicting nodal status based on other preoperatively available pathologic variables without compromising long-term outcomes is paramount. Therefore, the primary aim of this study was to devise a clinically applicable risk score for lymph node positivity for rectal neuroendocrine tumors using other preoperatively

known clinicopathologic factors that better discriminate lymph node involvement rather than tumor size alone.

2 | METHODS

2.1 | Data source and study variables

The National Cancer Database (NCDB) is a hospital-based registry, a joint program of the American College of Surgeons Committee on Cancer and the American Cancer Society, with data sources from more than 1500 Commission on Cancer-accredited hospitals.[16] A query of the NCDB registry from 2004 to 2014 was performed to identify patients with non-functional rectal neuroendocrine tumors according to International Classification of Diseases for Oncology-3 codes including 8240 (carcinoid not otherwise specific) and 8246 (neuroendocrine carcinoma). The analysis excluded patients with metastatic disease, palliative resections, or 30-day mortality. Patients were further excluded if they had missing data with regard to tumor size, pathologic T-stage, and pathologic lymph node status. Resection type was categorized as local resection (excisional biopsy in combination with polypectomy, curette/fulguration, and electrocautery) and formal/anatomic resection (low anterior resection, abdominoperineal resection, and Hartmann procedure). Tumor size was divided into three categories (<1, 1–2, and ≥2 cm). Patient demographics, clinicopathologic variables, and survival data were extracted. Tumor staging was based on the American Committee on Cancer (AJCC) 6th and 7th edition guidelines. The primary outcome was lymph node positivity after surgery. The secondary outcome was overall survival.

2.2 | Statistical analysis

Descriptive statistics for each variable were reported. The χ^2 test was used for comparison of discrete variables, and the analysis of variance test was used for comparison of continuous variables between the two cohorts. A Cox proportional hazards model was used to assess the association between clinicopathologic variables and survival. To create the Preoperative Rectal Stratification Score (PReSS), univariate logistic regression analysis was used to determine the association of clinicopathologic factors with lymph node positivity. Given the high accuracy of ERUS and MRI to assess depth of invasion preoperatively, pathologic T-stage was utilized as a surrogate for this information that would otherwise normally be readily available preoperatively. A multivariable model was then constructed using sequential backward selection. Variables statistically significantly associated with lymph node positivity ($P < .05$) on multivariable analysis were used to create PReSS. Each selected variable was assigned a score, from 0 to 2, based on the magnitude of the model coefficient. The incidence of lymph node positivity was determined for each combination of variables and groups were combined based on similar rates of lymph node involvement. These were incorporated to create a PReSS of four groups (0–3) associated with an increasing rate of lymph node positivity.

Kaplan-Meier analysis and Cox-regression analysis were used to determine the association of PReSS with overall survival. Statistical significance was pre-defined as two-tailed $P < .05$. All statistical analyses were conducted using SAS, version 9.4 (SAS Institute), and SAS macros developed at the Biostatistics and Bioinformatics at Winship Cancer Institute.[17]

3 | RESULTS

3.1 | Demographic and clinicopathologic characteristics

Among the 12384 patients with nonmetastatic rectal neuroendocrine tumors in the NCDB, a total of 383 patients met inclusion criteria (Figure 1). Demographic and histopathologic data are listed in Table 1. Mean patient age at diagnosis was 58 ± 12.4 years with a similar distribution of female (n = 183, 48%) and male (n = 200, 52%) patients. Mean tumor size was 2.1 ± 2.2 cm with 44% (n = 169) tumors measuring <1 cm, 16% (n = 61) tumors measuring 1–2 cm, and 40% (n = 153) tumors measuring ≥2 cm. On final pathologic analysis, the majority of patients had well-differentiated tumors (39%, n = 149), and pathologic T1 (submucosa) stage tumors (52%, n = 198). Median follow-up for the entire cohort was 45.3 months. Data on complications and recurrence were not available from the NCDB source to evaluate.

Among the entire cohort, 43% of patients had positive lymph nodes (n = 163). There were no significant differences between lymph node-negative and lymph node-positive patients when comparing patient characteristics including age at diagnosis, sex, race, and Charlson-Deyo score (all $P > .05$, Table 1). Compared to patients with negative lymph nodes, patients with positive lymph nodes had a larger proportion of ≥2 cm tumors (153 patients (40%) vs 48 patients (22%); $P < .01$), more poorly or undifferentiated tumors (57 patients (35%) vs 29 patients (13%); $P < .01$), a higher proportion of pathologic T3 (through muscularis propria) stage tumors (78 patients (48%) vs 19 patients (9%); $P < .01$), and were more likely to undergo an anatomic resection (158 patients (97%) vs 148 patients (67%); $P < .001$). On Cox regression for overall survival, lymph node positivity was associated with worse overall survival (HR 2.55, 95% CI 1.48–4.39, $P < .01$), even when accounting for other negative prognostic factors such as age older than 60 years and poorly or undifferentiated tumor grade.

3.2 | Prognostic factors for lymph node positivity

Clinicopathologic factors associated with lymph node positivity are listed in Table 2 and include age older than 60, tumor size ≥1 cm, moderate, poor or undifferentiated tumor grade, and pathologic T-stage past the submucosa. On multivariable binary logistic regression, two factors persisted as being associated with lymph node positivity and include tumor size ≥1 cm (1–2 cm: HR 4.24, 95% CI 2.08–8.65, $P < .01$; ≥ 2 cm: HR 3.61 95% CI 1.64–7.92, $P < .01$), and pathologic T-stage past the submucosa (T2—muscularis propria: HR 2.03, 95% CI 0.97–4.23, $P < .01$; T3—through muscularis propria: HR 7.41, 95% CI 3.28–16.83, $P = .06$, T4—adjacent organs: HR 4.08, 95% CI 1.29–12.91, $P = .02$)

3.3 | PReSS

When creating the PReSS, the two factors associated with increased odds of lymph node positivity were considered including tumor size (<1, 1–1.99, and ≥2 cm), and pathologic T-stage (T1: submucosa, T2: muscularis propria, T3: through muscularis propria, T4: adjacent organs) as each of these tumor characteristics can be determined pre-operatively by initial endoscopic evaluation and/or MRI. The incidence of lymph node positivity was determined for each combination of tumor size and depth of invasion and groups were then combined

based on similar rates of lymph node involvement (Table 3). Each factor was assigned a score from a scale of 0 to 2 points to create four risk groups 0 to 3 (tumor size: <1 cm—0 points, 1–1.99 cm—1 point, ≥2 cm—1 point, pathologic T-stage: T1 submucosa—0 points, T2 muscularis propria—1 point, T3 through muscularis propria—2 points, T4 adjacent organs—2 points). The percentage of patients with positive lymph nodes increased with increasing risk score: risk group 0 (0 points): 13% (n = 114/383), risk group 1 (1 point): 33%–42% (n = 54/383), risk group 2 (2 points): 50%–54% (n = 42/383), risk group 3 (3 points): 70%–83% (n = 110/383). Only two patients with invasion through the muscularis propria had tumors that were <1 cm, both of whom were lymph node negative, and no tumors invading into adjacent organs were <2 cm. Notably, when evaluating the entire cohort of 12 172 patients, there were only 12 patients that had <1 cm tumors invading through the muscularis propria, and 0 patients that had <2 cm tumors invading into adjacent organs, making these groups negligible.

3.4 | Association of PReSS with overall survival

On Kaplan-Meier analysis, there was a decreased 10-year overall survival with increase PReSS group (PReSS group 0: 90%; group 1: 81%; group 2: 59%; group 3: 41%, $P < .01$, Figure 2). Clinicopathologic factors significantly associated with worse overall survival are listed in Table 4 and include age older than 60 years, Charlson-Deyo score ≥2, poorly or undifferentiated tumor grade, positive resection margin status, and PReSS groups 2 and 3. On multivariable analysis, three factors persisted as being associated with worse overall survival and include age older than 60 years (HR 1.91, 95% CI 1.17–3.12, $P < .01$), poorly or undifferentiated tumor grade (HR 3.65, 95% CI 1.87–7.11, $P < .01$), PReSS group 2 (HR 5.47, 95% CI 1.50–19.98, $P = .01$), and PReSS group 3 (HR 8.61, 95% CI 2.53–29.22, $P < .01$).

4 | DISCUSSION

The rectum is one of the most common sites of gastrointestinal neuroendocrine tumors, and rectal neuroendocrine tumors have increased in incidence over the past decades, largely due to widespread use of screening colonoscopies.[18] Historically, rectal neuroendocrine tumors have demonstrated the best prognosis of all gastrointestinal neuroendocrine tumors with a 5-year survival of 96%.[19] However, it has been recognized recently that not all rectal neuroendocrine tumors behave in an indolent fashion, and prognosis is largely dependent on stage. Indeed, the AJCC staging classifies all node-positive colorectal neuroendocrine tumors as stage III, and according to a population-based study, the 5-year survival of stage III, node-positive tumors is only 35%.[2,20] Therefore, staging patients with the appropriate surgical resection is paramount to adequately educate patients on their prognosis and guide further treatment and surveillance strategies. Preoperative knowledge of lymph node positivity would serve to accurately select patients for either local or anatomic resection. Therefore, the aim of this study was to devise a clinically applicable risk score for lymph node positivity using other pre-operatively known clinicopathologic factors that better discriminate lymph node involvement rather than size alone. Our results are in accord with previous studies that have demonstrated the negative prognostic value on survival of lymph node positivity in rectal neuroendocrine tumors (HR 2.55, 95% CI 1.48–4.39, $P < .01$; Table

2). In the current study, two factors were strongly associated with lymph node positivity and included tumor size and depth of invasion. These two variables, which can be easily and accurately assessed preoperatively with an endorectal ultrasound or MRI, were incorporated into the PReSS which stratifies tumors into four risk groups (0–3) of progressively increasing lymph node positivity ranging from 11% to as high as 78% (PReSS group 0: 11%, group 1: 38%, group 2: 50%, group 3: 78%, $P < .01$, Table 4). Importantly, PReSS is also able to predict 10-year overall survival (PReSS group 0: 90%; group 1: 81%; group 2: 59%; group 3: 41%, Figure 2).

As lymph node metastases have demonstrated a negative prognostic role across most neuroendocrine tumor sites, including pancreas, and small bowel, various other studies have sought to predict nodal positivity with pre-operatively available clinicopathologic variables to guide patient management.[21] Our group recently demonstrated that for pancreatic neuroendocrine tumors, node positivity is associated with a worse 5-year recurrence-free survival with a minimum of seven lymph nodes required for adequate staging.[22] Similarly, small bowel neuroendocrine tumors have demonstrated aggressive behavior, and guidelines recommend radical resection for all tumors with routine lymphadenectomy.[23,24] Conversely, the role of lymphadenectomy for duodenal neuroendocrine tumors remains ill-defined and although regional nodal involvement may be common with increasing tumor size, the predictive value of lymph node metastases on long-term outcomes has not been proven.[25] In fact, the extent of resection for patients with duodenal neuroendocrine tumors remains controversial.[26] The ability to find an association between nodal status and long-term survival for this particular anatomic location may be hindered by this tumor's low incidence and indolent nature. Among nonfunctional rectal neuroendocrine tumors, the association between nodal involvement and poor outcomes has been clearly established with a recent study demonstrating worse survival with an increasing number of positive lymph nodes.[27,28] The current study supports these previous findings, with node-positive patients displaying a three-fold hazard ratio for overall survival compared to node-negative patients even when accounting for other negative prognostic factors. Currently, surgical resection represents the first-line therapy for rectal neuroendocrine tumors, but the extent of surgery is based solely on tumor size and further remains ambiguous for intermediate size tumors of 1 to 2 cm. Indeed, according to the NCCN guidelines, an endoscopic technique can be used for resection of tumors smaller than 1 cm while a radical resection is warranted for tumors larger than 2 cm.[13]

Unlike tumors of the midgut in which resection and lymphadenectomy may be performed with relatively minimal risk and morbidity, radical resection of rectal neuroendocrine tumors usually necessitates a low anterior resection or abdominoperineal resection, which can both be associated with much higher morbidity and decreased quality of life when compared to local resection alone. Indeed, leak rates after low anterior resection range from 10% to 36% in some studies, and this complication can further result in longer hospital length of stay and requirement for permanent stoma creation.[29,30] Similarly, abdominoperineal resection is associated with a high incidence of perineal wound complications which may result in chronic perineal fistulae, prolonged pain and wound care, and decreased quality of life.[31] Furthermore, the sequelae of both of these procedures in regard to urological and sexual dysfunction have been described in several studies.[32,33] Consequently, accurate preoperative

assessment of nodal status is paramount, and the findings from this study further highlight the importance of high quality ERUS and pelvic MRI for careful sizing and local staging of these tumors.

Previous data have attempted to identify prognostic tumor- specific factors to help guide operative management of rectal neuroendocrine tumors, however, studies have been limited by small cohorts and no consensus has been reached regarding the most accurate approach to risk-stratify these tumors.[28,34–36] Our data is powered by a larger sample, and although only 3% of patients had lymph nodes harvested, this highlights the inherent selection bias or clinical practice pattern to approach rectal neuroendocrine tumors in a non-oncologic manner. Indeed, a recent Surveillance, Epidemiology, and End Results Program study demonstrated that the majority of patients with rectal neuroendocrine tumors are undergoing local resection, with only 5% undergoing formal, anatomic excision.[37] According to PReSS, the incidence of lymph node positivity ranged from 11% to 78% which was higher than expected, but PReSS is able to accurately stratify patients as seen by each group's association with overall survival. Clearly, this risk score is identifying biologically aggressive tumors, regardless of size by taking into account depth of invasion. Specifically, PReSS identifies small-sized tumors with an increased depth that have higher rates of lymph node positivity than expected, and larger tumors with minimal penetration that have lower than expected lymph node-positive disease.

In the absence of data from randomized control trials, this risk score should be applied with various objectives. It should help guide discussions with patients regarding their risk of lymph node metastases, and options for excision including local vs formal resection in the context of each procedure's advantages and disadvantages when taking into account each patient's comorbidities. Additionally, this risk score should be applied when developing surveillance strategies after surgery as higher risk tumors that undergo local resection should be surveyed more closely.

The limitations of this study include those related to retrospective analysis and use of large databases such as potential coding errors, missing data, and the absence of several variables within the NCDB including mitotic rate, Ki-67 index, disease recurrence, and disease-specific survival. The lack of recurrence data poses a challenge when studying an indolent disease in which overall survival may not be an ideal outcome to evaluate its natural history. Additionally, our analysis only includes patients who had lymph nodes pathologically assessed after surgery, which introduces selection bias. Thirdly, while our analysis uses pathologic T-stage as a surrogate for preoperative ERUS/MRI depth of invasion, previous studies have demonstrated an accurate correlation.[6] Lastly, although the risk groups adequately predict overall survival, this risk score has not been externally validated and this poses an area of future study.

5 | CONCLUSION

For rectal neuroendocrine tumors, depth of invasion and tumor size predict lymph node positivity and both clinicopathologic variables can be readily obtained with a preoperative endoscopic ultrasound and/or MRI. This novel PReSS incorporates both variables and

stratifies tumors into four risk groups of progressively increasing lymph node positivity. Rather than tumor size alone, this score should be used to guide surgical approach as local resection alone will not yield lymph nodes and may lead to under-staging and anatomic resection may be preferred in patients with a higher risk for lymph node positivity.

ACKNOWLEDGMENTS

Research reported in this publication was supported in part by the Biostatistics and Bioinformatics Shared Resource of Winship Cancer Institute of Emory University and NIH/NCI under award number P30CA138292. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The data used in the study are derived from a de-identified NCDB file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed, or the conclusions drawn from these data by the investigator.

Funding information

National Center for Advancing Translational Sciences, Grant/Award Number: UL1TR002378/TL1TR002382

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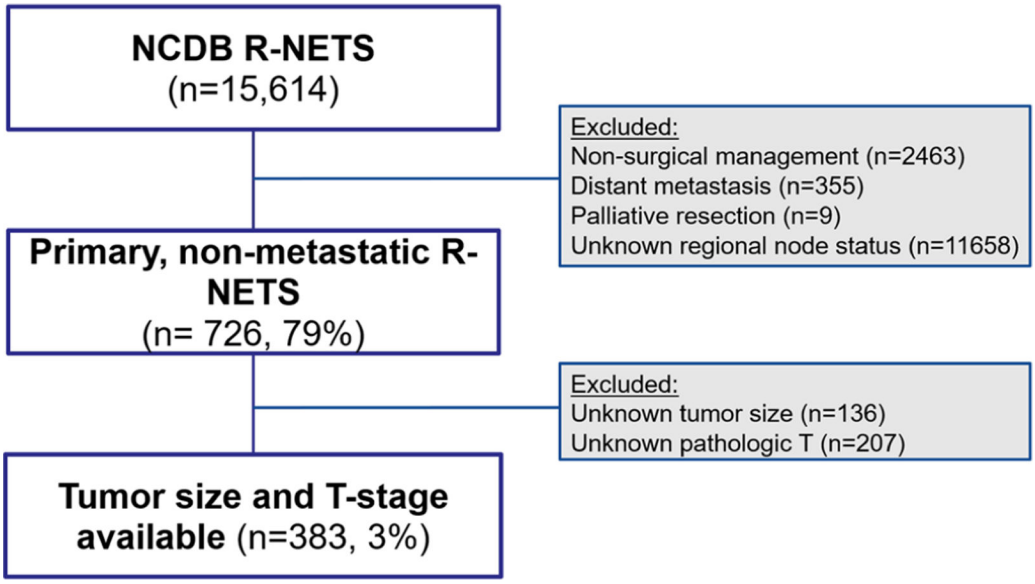

FIGURE 1.

Flow diagram of inclusion and exclusion criteria of patients in the National Cancer Database (NCDB) diagnosed with rectal neuroendocrine tumors. R-NETS, rectal neuroendocrine tumors

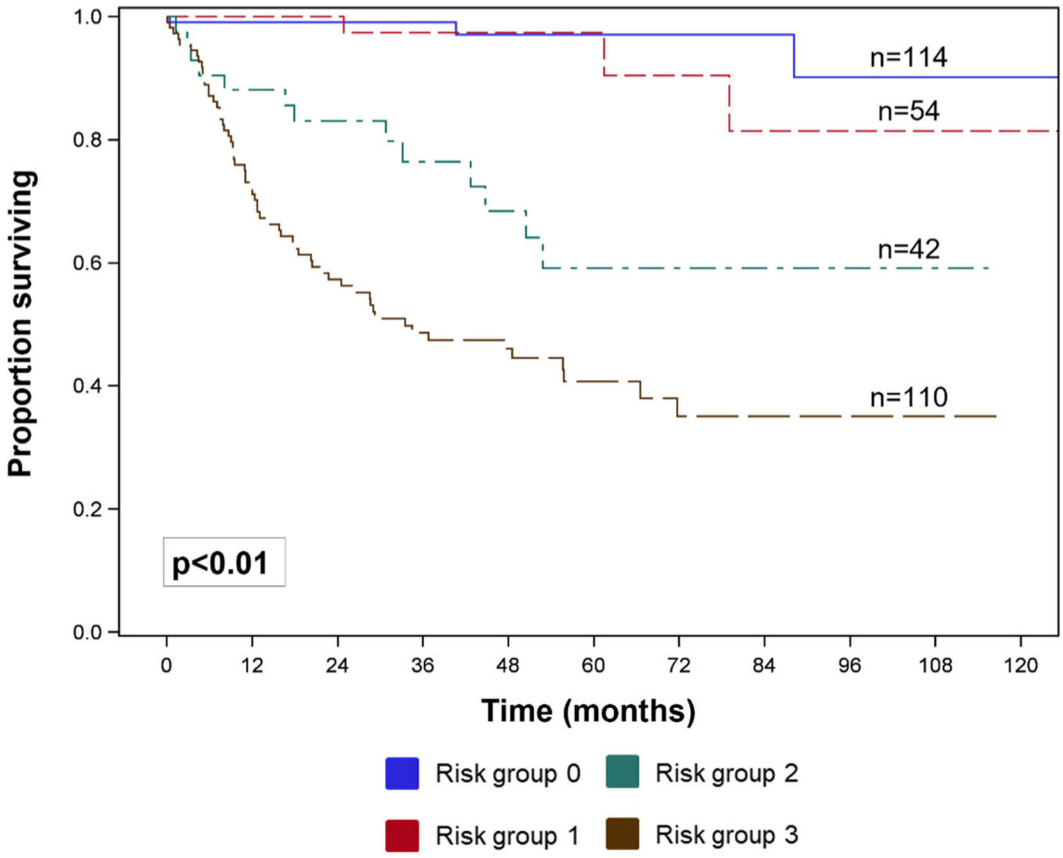

FIGURE 2.
Overall survival by PReSS, Preoperative Rectal Stratification Score risk groups

TABLE 1

Demographic and clinicopathologic factors of the entire cohort and comparing lymph node-negative vs lymph node-positive cohorts

	All patients n = 383 (%)	LN negative n = 220 (%)	LN positive n = 163 (%)	LN negative vs LN positive *P* value
Demographic variables				
Age at diagnosis (mean ± std)	58 ± 12.4	57 ± 11.9	59 ± 12.9	0.11
Sex				
Female	183 (48)	103 (47)	80 (49)	0.66
Male	200 (52)	117 (53)	83 (51)	
Race				
White	244 (64)	149 (68)	95 (58)	0.06
Non-white	183 (48)	71 (32)	68 (42)	
Charlson-Deyo score				
0	297 (78)	169 (77)	128 (79)	0.89
1	70 (18)	42 (19)	28 (17)	
2+	16 (4)	9(4)	7(4)	
Histopathologic factors Tumor size, cm				
<1	169 (44)	144 (65)	25 (15)	<0.01
1–1.99	61 (16)	28 (13)	33 (20)	
≥2	153 (40)	48 (22)	105 (64)	
Tumor differentiation				
Well	149 (39)	97 (44)	52 (32)	<0.01
Moderate	35 (9)	15 (7)	20 (12)	
Poor/undifferentiated	86 (22)	29 (13)	57 (35)	
Not determined	113 (30)	70 (32)	34 (21)	
AJCC pathologic T stage				
T1 (submucosa)	198 (52)	160 (73)	38 (23)	<0.01
T2 (muscularis propria)	65 (17)	34 (15)	31 (19)	
T3 (through muscular propria)	97 (25)	19 (9)	78 (48)	
T4 (adjacent organs)	23 (6)	7 (3)	16 (10)	
Type of Resection				
Local	77 (20)	72 (33)	5 (3)	<0.01
Anatomic	306 (80)	148 (67)	158 (97)	

	All patients n = 383 (%)	LN negative n = 220 (%)	LN positive n = 163 (%)	LN negative vs LN positive *P* value
Surgical margins				
Negative	323 (84)	191 (87)	132 (81)	<0.01
Positive	48 (13)	17 (8)	31 (19)	
Unknown	12 (3)	12 (5)	0(0)	
Follow-up (median, mo)	45.3	39	51.6	<0.001

Note: Percentages in parentheses are based on cohort size.

Abbreviations: AJCC, American Committee on Cancer; LN, lymph node.

Bold indicates statistical significance.

TABLE 2

Binary logistic regression: clinicopathologic factors associated with positive lymph node status

Variable	Univariable logistic regression		Multivariable logistic regression	
	OR (95% CI)	***P* value**	**OR (95% CI)**	***P* value**
Age at diagnosis, y				
≤60	Reference		-	
>60	2.15 (1.42–3.26)	<.01	-	
Sex				
Male	Reference		-	
Female	1.09 (0.73–1.64)	.66	-	
Race				
White	Reference		-	
Non-White	1.50 (0.99–2.29)	.06	-	
Charlson-Deyo score				
0	Reference		-	
1	1.03 (0.37–2.83)	.64	-	
2+	0.88 (0.52–1.50)	.96	-	
Tumor size, cm				
<1	Reference		Reference	
1–1.99	6.79 (3.51–13.12)	<.01	4.24 (2.08–8.65)	<.01
≥2	12.60 (7.31–21.73)	<.01	3.61 (1.64–7.92)	<.01
Tumor differentiation				
Well	Reference		-	
Moderate	2.49 (1.18–5.26)	.02	-	
Poor/	3.67 (2.09–6.42)	<.01	-	
undifferentiated				
Not determined	0.80 (0.48–1.36)	.41	-	
AJCC pathologic T				
T1 (submucosa)	Reference		Reference	
T2 (muscularis propria)	3.84 (2.10–7.01)	<.01	2.03 (0.97–4.23)	.06
T3 (through muscular propria)	17.28 (9.36–31.93)	<.01	7.41 (3.26–16.83)	<.01
T4 (adjacent organs)	9.62 (3.70–25.03)	<.01	4.08 (1.29–12.91)	.02

Note: Number of observations in the original data set = 383. Number of observations used = 383. Bold indicates statistical significance.

The logistic regression modeled the probability of LN = positive. Backward selection with an α level of removal of 0.05 was used. The following variables were removed from the model: age, sex, Charlson-Deyo score, and tumor differentiation.

Abbreviations: AJCC, American Committee on Cancer; CI, confidence interval; OR, odds ratio.

TABLE 3

Preoperative Rectal Stratification Score (PReSS) for lymph node positivity

	<1cm (0 points)	**1–1.99 cm (1 point)**	**≥2 cm (1 point)**
Submucosa (0 points)	13% (0 points)	42% (1 point)	33% (1 point)
Muscularis propria (1 point)	36% (1 point)	54% (2 points)	50% (2 points)
Through muscularis propria (2 points)	N/A	80% (3 points)	83% (3 points)
Adjacent organs (2 points)	N/A	N/A	70% (3 points)

TABLE 4

Clinicopathologic factors associated with overall survival for entire cohort

Variable	Univariable Cox regression		Multivariable Cox regression	
	HR (95% CI)	***P* value**	**HR (95% CI)**	***P* value**
Age at diagnosis, y				
≤60	Reference		Reference	
>60	3.07 (1.92–4.90)	**<.01**	1.91 (1.17–3.12)	**<.01**
Sex				
Male	Reference		-	
Female	1.13 (0.73–1.76)	.59	-	
Race				
White	Reference		-	
Non - White	2.06 (1.23–3.44)	.06	-	
Charlson-Deyo score				
0	Reference		-	
1	1.25 (0.72–2.19)	.43	-	
2+	2.51 (1.14–5.51)	**.02**	-	
Tumor differentiation				
Well	Reference		Reference	
Moderately	1.48 (0.48–4.58)	.05	1.32 (0.42–4.14)	.63
Poorly/	9.26	**<.01**	3.65	**<.01**
undifferentiated	(4.96–17.30)		(1.87–7.11)	
Not determined	0.55 (0.22–1.39)	.21	0.51 (0.20–1.31)	.16
Margin status				
Negative	Reference		-	
Positive	2.75 (1.63–4.63)	**<.01**	-	
PReSS risk group				
Group 0	Reference		Reference	
Group 1	1.97 (0.40–9.76)	0.41	1.35 (0.27–6.74)	.72
Group 2	11.70 (3.33–41.06)	**<.01**	5.47 (1.50–19.98)	**.01**
Group 3	25.49 (7.99–81.31)	**<.01**	8.61 (2.53–29.22)	**<.01**

Note: Number of observations in the original data set = 383. Number of observations used = 320. Bold indicates statistical significance. Backward selection with an α level of removal of .05 was used. The following variables were removed from the model: sex, Charlson-Deyo score, margin status.

Abbreviaitons: CI, confidence interval; HR, hazard ratio; PReSS, Pre-operative Rectal Stratification Score.