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Outcomes for a Large Cohort of Patients with Rectal Neuroendocrine Tumors: an Analysis of the National Cancer Database

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Abstract

Background—Rectal neuroendocrine tumors comprise 20% of neuroendocrine tumors in the alimentary tract, but there is controversy surrounding the optimal management of this disease. The purpose of this study is to better define treatment for patients with rectal neuroendocrine tumors.

Methods—Using the National Cancer Database, we analyzed patients with rectal neuroendocrine tumors between 2004 and 2015. Patients with metastatic disease and missing treatment data were excluded. We examined overall survival stratified by tumor size, treatment type, and presence of positive lymph nodes using Kaplan-Meier analysis with log-rank test. Cox proportional hazard regression model was performed to identify factors associated with overall survival.

Results—Intotal,17,448 patients withrectal neuroendocrinetumors wereidentified; 16,531ofthese patients metinclusion criteria. The majority of patients had tumors ≤ 10 mm (9216 patients, 79.8%), and approximately 90% underwent local excision. The probability of 5-year overall survival was significantly higher for patients with smaller tumors (≤ 10 mm: 94.1% 11–20 mm: 85.7%, > 20 mm: 71.8%; $p < 0.001$) and those with no positive lymph nodes (91.4% versus 53.3%, $p < 0.001$). The probability of 5-year overall survival differed based on treatment modality (local excision: 93.6%, radical resection: 79.1%, observation alone: 77.1%; $p < 0.001$). On multivariable Cox regression, when compared tolocal excision, radical resection was not

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Authors' Contributions All authors were involved in conception and design of the work.
Drs. Zhao and Eisenstein were involved in the acquisition of the data.
Drs. Zhao, Hollandsworth and Eisenstein were involved in analysis and interpretation of data.
Drs. Zhao and Hollandsworth were involved in drafting of the work.
All authors were involved in critically revision the manuscript for important intellectual content.
All authors gave final approval of the version to be published.
All authors agree to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriatey investigated and resolved.

Compliance with Ethical Standards

Conflict of Interest Dr. Eisenstein is a consultant for Auris Health.

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associated witha difference in overall survival but observation alone was associated with significantly worse OS (HR = 2.750, $p < 0.001$).

Conclusions—There is a significant difference in overall survival between patients who underwent local excision versus observation alone. Excision of the tumor should be offered to all patients with rectal neuroendocrine tumors who are appropriate surgical candidates, regardless of the tumor size.

Keywords

Colorectal; Neuroendocrine; Surgery; Outcomes

Introduction

Neuroendocrine tumors are derived from neural crest cells and most commonly arise in the bronchial tree and gastrointestinal tract.[1, 2] Rectal neuroendocrine tumors (rNETs) comprise 19.6% of all neuroendocrine tumors in the alimentary tract.[1] Recent reviews have suggested a significant increase in the incidence of rNET in the past three decades in the United States,[3–5] likely due to increased detection of asymptomatic and smaller lesions by increased utilization of endoscopic screening.[3, 6, 7]

Since rNETs are relatively rare, options for surgical management remain unclear.[2] Treatment options may include local excision, radical resection (including proctectomy), or observation alone. Tumor size is one of the most important prognostic factors and has been historically used as a guideline for surgical treatment.[8, 9] The current National Comprehensive Cancer Network (NCCN) guidelines for the treatment of rNETs are based on tumor size, margin status, and pathological grade.[10] These guidelines recommend radical resection for any tumor > 2 cm or with evidence of metastatic disease in any tumor size. For tumors < 2 cm, local excision may be considered.[10] Pathological staging and margin status play a role in the treatment algorithm for small tumors < 1 cm that are endoscopically resected.[10] Low-grade tumors with indeterminate margins may be observed with serial endoscopy at 6 months and it is recommended that tumors with indeterminate margins and intermediate grade undergo local excision.[10]

Previous studies have suggested that local excision is adequate for tumors of small size (< 1 cm), while radical resection is more appropriate for larger tumors.[8] Others have suggested that observation alone is sufficient for tumors < 1 cm.[11] Tumor size is also predictive of metastases, with tumors > 2 cm having higher metastatic potential.[7, 12] Further studies have suggested that tumors < 2 cm rarely metastasize,[13] making these tumors amenable to local excision. These conclusions are not without controversy, as other studies have suggested that tumor size is not reliable at predicting metastases and malignant potential of rNETs.[13] Lymph node (LN) metastases have been shown to be a predictor of poor prognosis, but are difficult to clinically determine LN status through current imaging techniques because LN size is a poor predictor of LN metastasis.[6] The varying results of small, single-institution studies and prior reviews complicate the interpretation of treatment recommendations and emphasize the need for clear guidelines for treatment of rNETs.

Previous studies addressing the treatment of rNETs have been mostly single-institution studies with small numbers of patients,[2, 14] which are prone to bias and have limited generalizability. In this study, we used a large nationwide oncologic database to better define the optimal treatment for patients with rNET by examining the role of patient-, disease-, and treatment-related factors on outcomes in patients with rNETs. The aim of the study is to bring clarity to the controversial treatment strategies of this rare disease by analyzing the outcomes based on treatment strategies of the largest cohort of patients with rNET to date.

Methods

A retrospective cohort study was performed using the National Cancer Database (NCDB). The NCDB, jointly sponsored by the American College of Surgeons and the American Cancer Society, is a national outcomes database that is focused on clinical oncologic data. The data is sourced from over 1500 Commission-on-Cancer (CoC) accredited centers and includes approximately 70% of all newly diagnosed cancer cases nationwide. Institutional Review Board exemption was granted for this study due to the de-identified nature of the data.

Patients diagnosed with rNET were identified by International Classification of Disease for Oncology histology codes 8240–8246. All patients diagnosed between 2004 and 2015 were included in this analysis. Patients with metastatic disease and those with missing treatment data were excluded. A CONSORT diagram is shown in Fig. 1. Patient age was categorized into rough quartiles(≤ 50,51–55,56–65,> 65years old). Race was categorized into white, black, American Indian, Asian/Pacific Islander, and other/unknown. Patient insurance status was categorized into private insurance, government insurance (including Medicare and Medicaid), no insurance, and unknown insurance status. The treatment center was dichotomized into academic versus non-academic centers (including community cancer, comprehensive community cancer, and integrated network cancer programs). Tumor size was categorized based on commonly accepted size cut-offs for rNETs: ≤ 10 mm, 11–20 mm, and > 20 mm. Patient comorbidity was measured by Charlson/Deyo comorbidity scores. Tumor grade was defined as well differentiated, moderately differentiated, poorly differentiated (including undifferentiated and anaplastic grades), and unknown grade. Pathologic examination of lymph nodes was dichotomized into yes/no. The presence of LN involvement was dichotomized into positive LNs versus non-positive LNs, which included negative and unknown lymph involvement. Resection margin status was dichotomized, with unknown resection margin status considered as a non-positive resection margin. Lastly, treatments were categorized into local excision (including polypectomy), radical resection (including any form of proctectomy and pull-through procedures), and observation alone. Of note, the surgical procedure coded in the NCDB is the most invasive procedure. For example, if a patient first underwent local excision followed by a radical resection, this would be coded as radical resection. Similarly, resection margins are coded as the final resection margin for the most invasive surgery. The primary outcome of interest is overall survival based on treatment modality. Overallsurvival(OS)wasutilizedastheprimaryoutcomesince disease-free survival cannot be determined by the NCDB. Secondary outcome of interest included OS based on lymph node involvement and tumor size due to their historic use in determining surgical treatment.

Categorical variables were compared using Chi-square test, while continuous variables were compared using MannWhitney U or Kruskal-Wallis tests. The log-rank test was used to compare OS as stratified by tumor size, treatment modality, and lymph node status. A Cox proportional hazard regression model was used to identify predictors associated with OS. First, a univariable analysis of possible predictors was done, with inclusion into the multivariable model set at a threshold of $p < 0.20$. From this, a multivariable Cox proportional hazard analysis was performed to identify independent predictors of OS. Patients with missing data were excluded from regression analysis. All analyses were performed using IBM SPSS Statistics (IBM Corporation, Version 24, Armonk, NY). All statistical tests were two-sided and the level of significance was set at 0.05 for all analysis.

Results

We identified a total of 17,448 patients with histology-proven rNET. A total of 16,531 patients satisfied our inclusion and exclusion criteria. Of those excluded, 189 had missing surgical procedure data and 732 had clinical metastatic staged disease. Four patients had both clinical metastatic stage disease and missing surgical data. Demographic information stratified by treatment can be seen in Table 1. The median age was 54, and 52.3% were female. The majority of patients had tumors ≤ 10 mm (9216 patients, 79.8%), while 1013 patients (8.8%) had tumors between 11 and 20 mm, and 1320 (11.4%) had tumors > 20 mm. Probabilities for 5-year OS was significantly higher for patients with smaller tumors (≤ 10 mm: 94.1% 11–20 mm: 85.7%, > 20 mm: 71.8%; $p < 0.001$).

A total of 2057 patients (12.4%) did not undergo a surgical procedure. Of the 14,474 who did have an operation, 13,126 (90.8%) underwent local excision of their rNET. Probabilities for 5-year OS were significantly different among the treatment options (local excision: 93.6%, radical resection: 79.1%, observation alone: 77.1%; $p < 0.001$).

The proportion of patients with any LNs pathologically examined and LN involvement differed by tumor size (Table 2). Stratified by tumor size, only 226/9000 (2.5%) of patients with tumors ≤ 10 mm had any LNs examined at all. Of these patients, 44/226 (19.5%) had positive LNs. For patients with tumors 11–20 mm in size, 126/983 (12.8%) had any LNs examined and 79/126 (62.7%) had positive LNs. Lastly, for patients with tumors > 20 mm in size, 309/1284 (24.1%) had any LNs examined and 213/309 (68.9%) had positive LNs. The 5-year OS for patients with positive LNs were significantly worse than for patients with non-positive LNs (53.3% versus 91.4%, $p < 0.001$).

The univariable and multivariable Cox proportional hazard ratio analysis can be seen in Table 3. After adjusting for multiple predictors, increasing age, increasing Charlson/Deyo comorbidity scores, moderately- and poorly-differentiated grade, increasing tumor size, positive LNs, and positive resection margins were associated with worse OS. Conversely, female gender, Asian/Pacific Islander race, and private insurance were associated with improved OS. Most importantly, after controlling for the above predictors, radical resection was not associated with a difference in OS compared to local excision, while observation alone was associated with significantly worse OS when compared to local excision (HR = 2.750, $p < 0.001$).

To further assess predictors for OS in among treatment options, we performed additional univariable and multivariable Cox regression models stratified by treatment cohorts. Supplemental Table 1 shows the results of the model that includes all patients with the lymph node status and resection margin status predictors excluded. Supplemental Table 2 shows the model that includes only patients who underwent local excision or radical resection, with the positive resection margin variable included. Lastly, Supplemental Table 3 shows the model that includes only patients who underwent radical resection, with both positive resection margin and positive lymph node status variables included.

Discussion

In the current study, we used the NCDB to perform the largest review of outcomes for patients with rNET. We found that most patients had tumors < 10 mm, and approximately 90% of all patients underwent local excision. OS was associated with tumor size, with smaller tumors having better OS compared to tumors > 20 mm. Surgical excision was associated with improved OS, with patients undergoing observation alone having the worst OS. There was no significant difference in OS between patients receiving local excision and radical resection regardless of tumor size. Patients with larger tumors were more likely to undergo examination of LNs and were more likely to have positive LNs, which was associated with worse OS.

There is considerable controversy in the treatment of rNET. A recent study suggested that observational management may offer equivalent OS to local excision or radical resection for small tumors less than 10 mm.[11] Conversely, a prior single-institution study challengedthis assertion after concludingthat local excision is more likely to lead to disease clearance than biopsy and observation alone,[15] suggesting that some form of surgical intervention provides better OS than observation. In the present study, we demonstrate that observation alone was associated with worse OS compared to local excision after controlling for tumor size. To assess the differences between surgical options in more depth, an analysis was performed to compare surgical options when lymph node status is excluded from the model, since lymph nodes are likely not examined during local excision. This model demonstrated a significant difference in overall survival between local excision and radical resection. However, this model may be subject to confounding as patients undergoing radical resection are more likely to have positive lymph nodes. In addition, lymph node positivity was associated with worse overall survival (see Supplemental Table 3). Therefore, it is important to control for lymph node status on multivariable analysis of all treatment options. In addition, while local excision appeared to have superior overall survival than radical resection in unadjusted Kaplan-Meier analysis, our adjusted multivariable model, which controlled for positive resection margins and positive lymph nodes, showed that there was no significant difference between the two approaches. However, even on multivariable Cox regression, no surgery had significantly worse overall survival. This suggests that surgical intervention should be considered in all patients with rNET.

Prior reports identified LN status as being an important predictor of survival.[1] Our data demonstrate that in patients with tumors 11–20 mm, 62.7% of patients who had LNs examined had positive LNs. For patients with tumors > 20 mm, 69.4% of those who had

LNs examined had positive LNs. This is consistent with previous studies that demonstrated that tumor size > 10 mm is significantly predictive of nodal involvement.[16–18] These results may be confounded by the fact that the likelihood of a patient receiving local excision decreases as tumor size increases. This is seen by the fact that 185/226 (81.9%) patients with tumors ≤ 10 mm who had lymph nodes examined underwent radical resection, while 295/309 (95.5%) patients with tumors > 20 mm underwent radical resection. In addition, technical aspects of local excision do not allow for LN status to be reliably determined and these patients likely had separate lymph node biopsy procedures to examine LN status. Patients with bigger tumors were more likely to undergo radical resection and, therefore, were more likely to have positive LNs identified. Selection bias may be present in all patients with rNETs because if they had concerning features on imaging or concern for positive LNs, they may have been offered radical resection.

In our study, patients undergoing local excision were significantly more likely to have a positive resection margin than patients undergoing radical resection. However, positive margin status has been a controversial topic in the treatment of rNETs. As previously discussed, current NCCN guidelines recommend surgical intervention for tumors < 1 cm with indeterminate margins after biopsy and intermediate grade on pathologic examination.[10] A prior small single-institution study demonstrated that nearly all patients with positive margins after endoscopic biopsy did not have recurrence of disease or residual disease on follow-up biopsy,[15] which suggests that observation alone may be adequate regardless of margin status. In the present study, we demonstrate that positive resection margins are associated with worse OS on univariable and multivariable analysis, but after controlling for margin status, local excision had no difference in OS compared to radical resection.

Current NCCN guidelines recommend local excision for tumors < 2 cm in size and radical resection (including low anterior resection and abdominoperineal resection) for tumors > 2 cm insize.[9] For small tumors < 1 cm withpositive margins and indeterminate pathological grade, local excision is recommended.[10] Observation is currently only recommended for tumors < 1 cm with negative margins after endoscopic biopsy.[10] Our results suggest that the current guidelines are not being followed in all practices, since 68.8% of patients who underwent radical resection had tumors < 20 mm and only 31.2% of patients with tumors ≥ 20 mm underwent radical resection. This may be explained by patient selection from surgeons or patient preference, both of which cannot be controlled for with available information in the NCDB database. Surgeon preference may also play a role in the treatment plan chosen for patients with rNET. Since rNETs are relatively rare compared to other tumor types, surgeons may have limited experience with rNETs and therefore have limited knowledge of the current recommended guidelines.

Our study is limited by its retrospective nature, which can limit the variables available for analysis. For example, the NCDB does not contain Ki-67 index and mitoses per highpowered field data, which indices are currently used to grade rNET.[19] Instead, the NCDB relies on differentiation for grade. In addition, almost 60% of patients had an unknown grade designation. The reason for this unknown but may be related tothe sample procedure used, asthere is a higherproportion of unknown grade in patients undergoing observation alone and lower proportion in patients undergoing radical resection.

Unfortunately, disease-specific survival and local recurrence rates cannot be assessed using the NCDB, only overall survival. The NCDB does not differentiate between endoscopic excision versus trans-anal excision; both are considered local excision. The NCDB also does not collect specific data on chemotherapy regimen. In addition, in the NCDB, lymph nodes are defined as positive on pathologic examination without clear indication of how the lymph nodes were examined or obtained. This may introduce bias in the conclusions drawn from the cohort ofpatients withpositivelymph nodes. We also cannot assess surgical decision-making, including patient preferences and surgical candidacy. Retrospective reviews also do not provide insight on surgeon experience with the disease of interest and surgeon preference or bias towards specific treatment types. Since we are limited by the data available in the NCDB, we are unable to completely adjust for all factors that would place patients in a high-risk category, which limits the conclusions we are able to draw from analysis. The retrospective nature of the study also makes it difficult to draw conclusions on cause and effect of risk factors and outcomes. Lastly, the NCDB only contains patients treated at CoCaccredited centers, which may limit generalizability. To date, there have been no prospective studies assessing the outcomes and overall survival of different treatment options for patients with rNET. Prospective studies could provide further information on outcomes and predictors of survival as well as clinical information that influencessurgical decision-making,which is inherently missing in retrospective database reviews.

Conclusion

With increasing rates of the diagnosis of rNET due to improvements in endoscopic surveillance,[3, 6, 7] it is critical to establish clear guidelines for surgical treatment of these tumors. We conclude that there is a significant difference in overall survival between patients who underwent local excision versus those who underwent observation alone. Therefore, excision of the tumor should be offered to all patients with rectal carcinoid tumors who are appropriate surgical candidates, regardless of the tumor size. Since OS is improved in local excision, this surgical approach should be considered where appropriate, but radical resection may have to be considered when there is concern for high-risk factors. A prospective study could better define treatment guidelines for patients with rectal carcinoid tumors. However, given rNET's rarity, accrual to a study such as this may be challenging.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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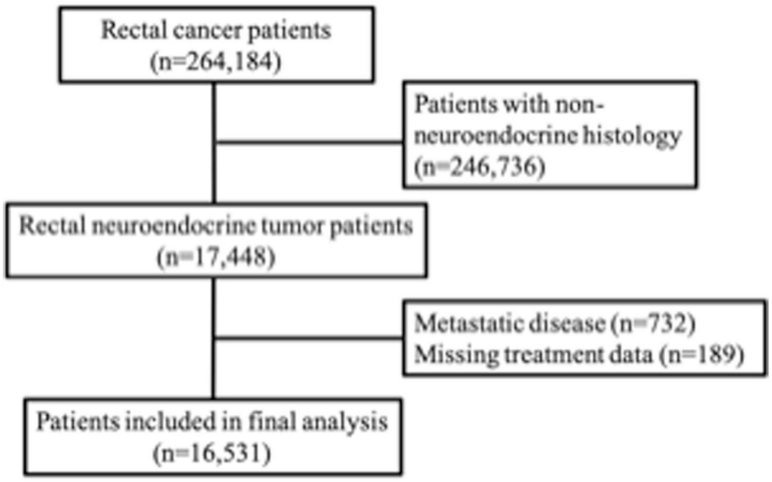

Fig. 1.
CONSORT diagram

Table 1

Patient demographics stratified by treatment

Variables	All patients	Observation alone	Local excision	Radical resection	*p* value[a]
Number of patients	16,531	2057 (12.4)	13,126 (79.4)	1348 (8.2)	
Median age	54	56	54	55	< 0.001
δ50	5132 (31.0)	583 (28.3)	4125 (31.4)	424 (31.5)	
51–55	3819 (23.1)	419 (20.4)	3142 (23.9)	258 (19.1)	
56–65	4475 (27.1)	562 (27.3)	3554 (27.1)	359 (26.6)	
> 65	3105 (18.8)	493 (24.0)	2305 (17.6)	307 (22.8)	
Female sex	8644 (52.3)	1018 (49.5)	6932 (52.8)	694 (51.5)	0.016
Race					< 0.001
White	9821 (60.9)	1156 (58.0)	7780 (60.7)	885 (67.1)	
Black	4827 (29.9)	691 (34.7)	3821 (29.8)	315 (23.9)	
American Indian	67 (0.4)	6 (0.3)	56 (0.4)	5 (0.4)	
Asian/Pacific Islander	1204 (7.5)	113 (5.7)	991 (7.7)	100 (7.6)	
Other	209 (1.3)	28 (1.4)	167 (1.3)	14 (1.1)	
Charlson/Deyo comorbidity Score					< 0.001
0	14,022 (84.8)	1698 (82.5)	11,213 (85.4)	1111 (82.4)	
1	1986 (12.0)	268 (13.0)	1526 (11.6)	192 (14.2)	
2	376 (2.3)	56 (2.7)	286 (2.2)	34 (2.5)	
ε3	147 (0.9)	35 (1.7)	101 (0.8)	11 (0.8)	
Insurance status					< 0.001
Private	10,468 (63.3)	1120 (54.4)	8490 (64.7)	858 (63.6)	
Government	5168 (31.3)	763 (37.1)	3967 (30.2)	438 (32.5)	
None	574 (3.5)	102 (5.0)	437 (3.3)	35 (2.6)	
Unknown	321 (1.9)	72 (3.5)	232 (1.8)	17 (1.3)	
Treatment at an academic center	5473 (36.0)	636 (33.7)	4345 (36.0)	492 (39.9)	0.002
Tumor size					< 0.001
δ10 mm	9216 (79.8)	698 (69.7)	7959 (84.1)	559 (51.7)	
11–20 mm	1013 (8.8)	73 (7.3)	755 (8.0)	185 (17.1)	
> 20 mm	1320 (11.4)	230 (23.0)	752 (7.9)	338 (31.2)	

Variables	All patients	Observation alone	Local excision	Radical resection	*p* value[a]
Clinical N stage					< 0.001
cN0	6995 (42.3)	576 (29.1)	6004 (47.1)	415 (31.6)	
cN1	2109 (12.8)	423 (21.4)	1246 (9.8)	440 (33.5)	
cNx	6928 (41.9)	982 (49.6)	5487 (43.1)	459 (34.9)	
Tumor grade differentiation					< 0.001
Well	5542 (33.5)	513 (24.9)	4580 (34.9)	449 (33.3)	
Moderate	701 (4.2)	62 (3.0)	520 (4.0)	119 (8.8)	
Poor/anaplastic	385 (2.3)	157 (7.6)	49 (0.4)	179 (13.3)	
Unknown	9903 (59.9)	1325 (64.4)	7977 (60.8)	601 (44.6)	
Positive resection margins	–	–	1302 (9.9)	107 (7.9)	< 0.001

[a]By Kruskal-Wallis or Chi-square test

Table 2

Number of patients with lymph nodes pathologically examined and positive lymph nodes stratified by tumor size

Lymph nodes pathologically examined (%)			
Tumor size	**All patients**	**Radical resection patients only**	**Patients with positive lymph nodes (%)**
δ10 mm	226/9000 (2.5)	185/549 (33.7)	44/226 (19.5)
11–20 mm	126/983 (12.8)	114/184 (62.0)	79/126 (62.7)
> 20 mm	309/1284 (24.1)	295/335 (88.1)	213/309 (68.9)

Table 3

Cox regression for predictors of overall survival

Predictors		Univariable *P* value hazard ratio 95% CI		Multivariable *P* value hazard ratio 95% CI		
Patient age						
δ50	Ref.	–	–	Ref.	–	–
51–55	0.105	–	–	0.506	–	–
56–65	< 0.001	2.193	1.864–2.580	< 0.001	1.685	1.343–2.114
> 65	< 0.001	6.625	5.711–7.685	< 0.001	2.994	2.367–3.788
Female gender	< 0.001	0.726	0.658–0.800	< 0.001	0.759	0.667–0.863
Patient race						
White	Ref.	–	–	Ref.	–	–
Black	0.002	1.177	1.060–1.307	0.149	–	–
American Indian	0.657	–	–	0.085	–	–
Asian/Pacific Islander	< 0.001	0.468	0.355–0.617	0.002	0.566	0.395–0.810
Other/unknown	0.407	–	–	0.556	–	–
Patient insurance						
Private	Ref.	–	–	Ref.	–	–
Government	< 0.001	4.195	3.779–4.657	< 0.001	1.926	1.625–2.283
None	< 0.001	2.636	2.045–3.397	< 0.001	2.620	1.890–3.633
Unknown status	< 0.001	2.121	1.514–2.971	0.043	1.608	1.016–2.547
Treatment at an academic center	0.192	–	–	0.308	–	–
Charlson/Deyo comorbidity score						
0	Ref.	–	–	Ref.	–	–
1	< 0.001	2.202	1.941–2.498	< 0.001	1.565	1.329–1.843
2	< 0.001	4.281	3.495–5.243	< 0.001	2.950	2.274–3.828
ε3	< 0.001	7.725	5.892–10.129	< 0.001	4.881	3.434–6.937
Tumor grade						
Well-differentiated	Ref.	–	–	Ref.	–	–
Moderately differentiated	< 0.001	1.724	1.311–2.267	0.042	1.408	1.012–1.961
Poorly differentiated	< 0.001	21.480	18.097–25.495	< 0.001	4.877	3.749–6.344
Grade unknown	0.010	1.194	1.043–1.366	0.322	–	–

Predictors		Univariable *P* value hazard ratio 95% CI		Multivariable *P* value hazard ratio 95% CI		
Tumor size						
≤ 10 mm	Ref.	–	–	Ref.	–	–
11–20 mm	< 0.001	2.584	2.157–3.096	< 0.001	2.081	1.721–2.515
> 20 mm	< 0.001	5.168	4.511–5.922	< 0.001	2.099	1.753–2.513
Positive lymph nodes	< 0.001	6.290	5.372–7.366	< 0.001	2.419	1.856–3.151
Positive resection margins	< 0.001	1.332	1.139–1.558	0.014	1.275	1.051–1.547
Treatment						
Local excision	Ref.	–	–	Ref.	–	–
Radical resection	< 0.001	3.105	2.712–3.554	0.683	–	–
Observation alone	< 0.001	3.484	3.103–3.912	< 0.001	2.750	2.296–3.293