Regional lymph node involvement and outcomes in appendiceal neuroendocrine tumors: a SEER database analysis.

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BACKGROUND

- Appendiceal neuroendoctine tumors (NETs) are usually discovered incidentally during appendectomy.
- This decision to proceed with right hemicolectomy (i.e. RHC) is usually based on an assessment of the risk of regional LN involvement and/or metastatic disease.
- Based on small retrospective studies, tumors with size >20 mm are thought to require RHC.
- The 20-mm cutoff has been widely accepted and used to formulate current treatment guidelines for RHC.
- However, the impact of RHC on survival is unknown, especially in appendiceal well differentiated NETs (WDNET), who usually have an excellent prognosis.

STUDY AIMS

We aimed to investigate:

- Association between the tumor size and the risk of nodal metastases.
- Association of type of surgery (appendectomy versus RHC) with cancer-specific survival in each histologic subtype.

PATIENTS AND METHODS

- Data were collected from the SEER database (November 2014 submission).
- Histology codes were obtained from the ICD 3rd edition for Oncology and were grouped according to the 2010 WHO classification into WDNETs, poorly differentiated neuroendocrine carcinomas (PDNECs) and mixed histology tumors (MHTs).
- MANEC is defined as a tumor with both neuroendocrine and epithelial components when each component constitutes greater than 30% of neoplastic tissue. Since the ratio of the histologic components has not been recorded in SEER database, we classified tumors with both neuroendocrine and epithelial components as "Mixed histology tumors (MHTs)".

Evaluation of association between tumor size and LN involvement in each histologic subtype

- Node-positive disease was defined as any pathologic LN involvement, regardless of the number of examined LNs.
- Node-negative disease was defined as if there was no nodal involvement after surgical examination of ≥12 LNs

Evaluation of association between type of surgery and cancer-specific survival

- The staging basis for LN involvement was clinical.
- Surgical treatment was categorized as no surgery, local surgery, and RHC.

RESULTS

Appendiceal NET histologic subtypes

(cases 1998-2012)

Tumor type	Histology Code	Definition	N
WDNET (n=860)	8240/3	Neuroendocrine tumor, low grade	643
	8241/3	Enterochromaffin cell carcinoid	14
	8246/3	Neuroendocrine carcinoma, NOS (G*1/2)	188
	8249/3	Neuroendocrine tumor, G2	15
PDNEC (n=26)	8013/3	Large cell neuroendocrine carcinoma	*
	8041/3	Small cell carcinoma, NOS	*
	8246/3	Neuroendocrine carcinoma, NOS (G3/4)	*
MHT (n=1659)	8243/3	Goblet cell carcinoid	911
	8244/3	Mixed adenoneuroendocrine carcinoma	247
	8245/3	Adenocarcinoid tumor	501

Demographic and clinicopathologic features

(cases 2004-2012)

Variable	No. of patients (%)		p
	WDNET	MHT	
	n=658	n=1052	
Age at diagnosis	Median: 42 y	Median: 56 y	<0.001
Sex	n=658	n=1052	
Female	418 (63.5)	516 (49.0)	<0.001
Male	240 (36.5)	536 (51.0)	
Race	n=642	n=1052	
White	565 (88.0)	922 (87.6)	0.75
Black	45 (7.0)	82 (7.8)	
Other	32 (5.0)	48 (4.6)	
Tumor size	n=571	n=660	<0.001
≤10 mm	296 (51.8)	177 (26.8)	
11–20 mm	164 (28.7)	178 (26.9)	
>20 mm	111 (19.4)	305 (46.2)	
Nodal metastases	n=616	n=1005	
No	490 (79.5)	825 (82.1)	0.21
Yes	126 (20.5)	180 (17.9)	
Distant metastases	n=622	n=1015	
No	592 (95.1)	890 (87.7)	<0.001
Yes	30 (4.8)	125 (12.3)	

RESULTS

Association between tumor size and regional LN

	WDNET	MHT	PDNEC
	No. LN-positive/No. patients examined (%)		
Tumor size	n=194	n=316	N=13
≤10 mm	11.6 (5/43)	10.4 (5/48)	0
11–20 mm	56.8 (42/74)	32.9 (27/82)	0 (0/1)
>20 mm	76.6 (59/77)	46.2 (86/186)	91.6 (11/12)

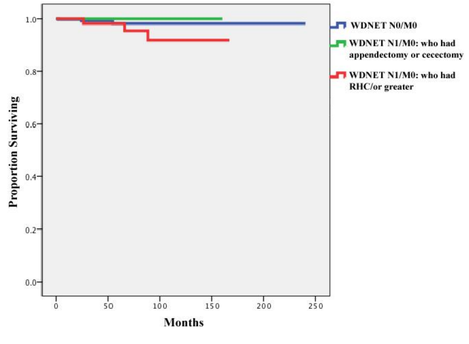
- Higher rates of LN involvement were noted in 11-20 mm tumors than in smaller tumors. WDNETs, 56.8% vs. 11.6%, *p* <.001; MHTs, 32.9% vs. 10.4%, *p* =.004

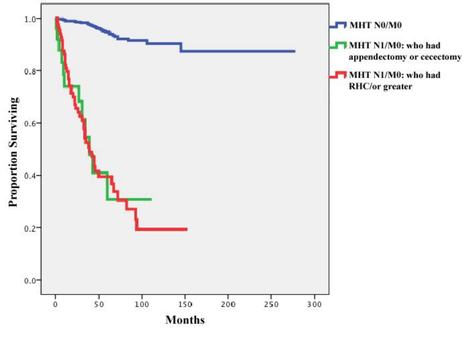
Associations between type of surgery and cancer-specific survival

	Univariate Analysis		Multivariate Analysis	
Factors	HR (95% CI)	*p*	HR (95% CI)	*p*
Histologic Subtype				
WDNET(n=674)	-Ref-		-Ref-	
MHT(n=1067)	3.60 (2.28-5.68)	<.001	15.77 (6.81-36.53)	<.001
Age at diagnosis				
≤65 years old	-Ref-		-Ref-	
>65 years old	3.52 (2.55-4.87)	<.001	2.18 (1.42-3.36)	<.001
Sex				
Male	-Ref-		-Ref-	
Female	1.30 (0.97-1.75)	0.08	1.23 (0.83-1.82)	0.30
Race				
Whites	-Ref-		-Ref-	
Blacks	1.62 (1.06-2.47)	0.03	1.09 (0.61-1.96)	0.77
Others	1.14 (0.53-2.43)	0.73	1.14 (0.41-3.17)	0.80
Node Involvement				
No	-Ref-		-Ref-	
Yes	6.95 (5.05-9.58)	<.001	11.41 (7.64-17.04)	<.001
Surgery Type				
Local surgery	-Ref-		-Ref-	
RHC/or greater	1.82 (1.24-2.67)	<.001	1.12 (0.72-1.73)	0.62

RESULTS

Cancer-specific survival according to nodal and type of surgery





DISCUSSION

- This is the first study comparing the effects of extensive surgery in patients with regionally advanced appendiceal NETs.
- Tumor size of 10 mm is a more appropriate predictive threshold than 20 mm for predicting LN involvement in WDNETs.
  - ✓ Lower incidences of LN involvement have been reported in prior studies. Prior studies used the broad definition of "carcinoid tumor" of appendix while, we implemented the most recent WHO classification to define WDNETs. In addition, in contrast to these studies, only cases with available data for pN0/or pN1 were included. Finally, cases were counted as node-negative only if they had adequate LN dissection (defined as at least 12 LN examined, extrapolating from colon cancer data given anatomical proximity and similar surgical techniques).
- While patients with WDNETs have a favorable prognosis even when they have nodal metastases, patients with MHTs—despite their lower overall rate of nodal metastases- have dramatically lower survival rates when they have LN metastasis.
- PDNECs are almost always discovered when they have grown larger than 10 mm and harbor a significant risk of both nodal and distant metastases.
- Patients with WDNETs had favorable overall outcomes in our study irrespective of LN involvement.
- Patients with MHTs and LN involvement overall have significantly worse outcomes compared to WDNETs and that also RHC does not improve outcomes. The role of post-operative adjuvant chemotherapy remains to be determined.

SUMMARY

- In summary, this study suggests that WDNETs have a much higher rate of nodal metastasis in tumors sized 11–20 mm than previously shown.
- The cancer-specific survival for WDNETs is generally favorable, and does not seem to be further improved by RHC. Therefore, appendectomy may be considered an adequate treatment option for select WDNET cases even in the presence of nodal metastases.
- Conversely, in patients with MHTs, outcome is significantly worsened by LN involvement. Future studies should evaluate the role of adjuvant chemotherapy in this subgroup.

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