Annals of Diagnostic Pathology 46 (2020) 151485

Contents lists available at ScienceDirect

Annals of Diagnostic Pathology

journal homepage: www.elsevier.com/locate/anndiagpath

Original Contribution

Gross tumor size using the AJCC 8th ed. T staging criteria does not provide prognostic stratification for neoadjuvant treated pancreatic ductal adenocarcinoma

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ARTICLE INFO

Keywords:
Pancreatic ductal adenocarcinoma
Neoadjuvant therapy
Staging
AJCC
Gross tumor size

ABSTRACT

The 8th edition AJCC T stage criteria for pancreatic ductal adenocarcinoma (PDAC) are now size based. These criteria provide better prognostic stratification in patients without neoadjuvant therapy. Our aim was to determine if gross tumor size is prognostically significant using the 8th ed. staging criteria for neoadjuvant treated PDAC. The study included 289 patients who underwent resection for PDAC following neoadjuvant therapy. By AJCC 7th ed., there were 12 (4.2%) ypT0, 32 (11.1%) ypT1, 64 (22.1%) ypT2, and 181 (62.6%) ypT3 patients. By AJCC 8th ed., there were 12 (4.2%) ypT0, 74 (25.6%) ypT1 (6 ypT1a, 1 ypT1b, 67 ypT1c), 161 (55.7%) ypT2, and 42 (14.5%) ypT3 patients. 182 patients had negative lymph nodes and 107 had positive lymph nodes. 77 patients were ypN1 and 30 were ypN2 by 8th ed. criteria. 7th ed. T stage significantly correlated with OS ($p = 0.048$), while 8th ed. T stage did not correlate with OS ($p = 0.13$). In ypN0 patients, neither the 7th ed. or 8th ed. T stages significantly correlated with patient OS ($p = 0.065$ and 0.26, respectively). Higher 7th ed. T stage correlated with lymph node status ($p \leq 0.001$) more strongly than 8th ed. T stage ($p = 0.04$). 7th ed. and 8th ed. N stage correlated with OS ($p = 0.004$ and $p = 0.0002$, respectively). By 8th ed. AJCC staging criteria, gross tumor size does not provide good prognostic stratification in neoadjuvant therapy PDAC. Mapped grossing techniques combining gross and microscopic examination to determine tumor size may provide more accurate staging of neoadjuvant treated tumors.

1. Introduction

The American Joint Committee on Cancer (AJCC) recently updated the tumor (T) and lymph node (N) staging criteria (8th edition) for pancreatic ductal adenocarcinoma (PDAC). The 7th edition T stage criteria for PDAC were partially based on the extent of tumor spread. The 8th edition T stage criteria are now primarily size based (Table 1). The major change was in the T3 group, which by 7th ed. criteria included tumors of any size that had extrapancreatic extension without involvement of the celiac axis or superior mesenteric artery [1]. The 8th ed. T3 stage group now includes all tumors that are larger than 4 cm in greatest dimension without involvement of the celiac axis or superior mesenteric artery [2]. The T stage criteria were updated because of several problems with the 7th ed. criteria. The first was that determination of extrapancreatic extension (EPE) is quite subjective, largely because the pancreas does not have a true capsule [3,4]. In the setting of PDAC, the border between pancreatic and extrapancreatic tissue can be obscured by fibrosis making the distinction between pancreatic and extrapancreatic tissue even more difficult. Secondly, detection of EPE is dependent upon the level of sampling of the pancreas. In one study, 95.5% of tumors were classified in the T3 group (7th edition) [5-7]. With the vast majority of tumors classified in the T3 group, the 7th edition staging system had limited prognostic utility.

Tumor size has been identified as a significant prognostic factor for PDAC in several studies [6,8,9]. The 8th ed. size cutoffs were based on these studies and were subsequently validated in multi-institutional and SEER data based studies [10,11]. Further, it was shown that the 8th ed. T stage criteria distribute patients more evenly among stage groups and are more reproducible between institutions and pathologists than the previous criteria [10]. However, these validation studies excluded patients who received neoadjuvant therapy prior to resection and they did not use a uniform method of measuring tumor size (Table 2). Chatterjee

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https://doi.org/10.1016/j.anndiagpath.2020.151485

Table 1
7th edition versus 8th edition AJCC T stage criteria for pancreatic carcinoma.

	AJCC 7th edition	AJCC 8th edition
pT0	No evidence of primary tumor	No evidence of primary tumor
pTis	Carcinoma in situ	Carcinoma in situ
pT1	Tumor limited to the pancreas, ≤2 cm in greatest dimension	Tumor ≤2 cm in greatest dimension pT1a: Tumor ≤0.5 cm in greatest dimension pT1b: Tumor > 0.5 cm and < 1 cm in greatest dimension pT1c: Tumor 1–2 cm in greatest dimension
pT2	Tumor limited to the pancreas, > 2 cm in greatest dimension	Tumor > 2 cm and ≤ 4 cm in greatest dimension
pT3	Tumor extends beyond the pancreas without involvement of the celiac axis or the superior mesenteric artery	Tumor > 4 cm in greatest dimension
pT4	Tumor involves the celiac axis or the superior mesenteric artery	Tumor involves the celiac axis, superior mesenteric artery, and/or common hepatic artery

Table 2
Summary of literature: studies that have investigated whether AJCC 8th edition T stage correlates with survival.

Study	NeoTx?	Correlation with survival?		Method of size measurement
		AJCC 7th ed.	AJCC 8th ed.	
Current study	Yes	Yes	No	Gross only
Chatterjee et al. [12]	Yes	Yes	Yes	Gross with microscopic correlation
Shin et al. [20]	No	Yes	Yes	Gross only
Song et al. [21]	No	Yes	Yes	Not specified
Allen et al. [10]	No	Yes	Yes	Gross ± microscopic assessment

and colleagues recently assessed the prognostic significance of the 8th ed. T stage criteria in a cohort of patients who underwent pancreatic resection after receiving neoadjuvant therapy. They used a more labor-intensive mapped grossing approach to determine tumor size and showed that the 8th edition T stage correlates with lymph node metastasis, disease-free survival, and overall survival. They conclude that the 8th edition criteria stratify patients with PDAC resected after neoadjuvant therapy better than the 7th edition criteria [12]. However, many institutions and prior studies have not used a mapped gross technique for pancreatic resections and they rely on tumor size measured by gross examination, owing to its simplicity. Reliance on gross tumor size may be particularly problematic in tumors resected after neoadjuvant therapy because treatment can induce chronic pancreatitis in the background pancreas which further obscures the tumor bed, complicating the already difficult task of grossly distinguishing tumor bed from adjacent pancreas [13]. The aim of this study was to determine if the 8th edition AJCC T stage based on gross tumor size provides prognostic stratification for PDAC resected after neoadjuvant therapy.

2. Methods

After obtaining approval from the institutional review board we searched an institutional oncology database for patients who underwent pancreatic resection (pancreaticoduodenectomy or distal pancreatectomy) after receiving neoadjuvant therapy for PDAC between 2009 and 2017 (n = 294). Patient demographic information and survival data were collected from the database. Gross tumor size, lymph node status, and original T and N stage (AJCC 7th ed.) were collected from the corresponding pathology reports. Cases without a documented gross tumor size were excluded from the study (n = 5). In four of the excluded cases, no gross tumor was identified and tumor was only identified on microscopic examination. The one other excluded case was a large (12.5 cm) intraductal papillary mucinous neoplasm with focal invasive carcinoma which was only detected microscopically and therefore no invasive tumor was grossly identified.

Gross tumor sizes collected from the pathology reports were used to assign T stages based on AJCC 8th edition criteria. A standardized gross protocol was not in use during the study period. Microscopic tumor size was only utilized to assign T stage if the tumor was entirely submitted for microscopic examination and the only focus of residual tumor was present on one slide or if a mass was grossly identified but no residual microscopic tumor was present (ypT0 cases). Overall survival was measured from the date of diagnosis to the date of death. Progression free survival was measured from the date of surgery to the date of tumor progression. Kaplan-Meier survival curves for overall survival and progression free survival were constructed and compared using the log-rank test. Chi-square analysis was used to compare categorical variables. Statistical tests were performed using SPSS software (MedCalc, Version 18.11.3; MedCalc Software, Ostend, Belgium).

3. Results

3.1. Patient demographics and treatment details

289 patients who underwent pancreatic resection after receiving neoadjuvant therapy for pancreatic ductal adenocarcinoma were included in the study. The patients had a mean age of 65.9 years (range: 38 to 87 yrs.). 150 patients were women and 139 were men (M:F 0.9). 118 patients (41%) underwent neoadjuvant 5-FU based chemotherapy, 62 patients (21%) gemcitabine based chemotherapy, 13 patients (4%) 5-FU based chemoradiation therapy, 87 patients (30%) gemcitabine based chemoradiation therapy, 8 patients (3%) capecitabine based chemotherapy, and one patient underwent an unknown regimen of chemoradiation therapy.

3.2. Staging data

The mean gross tumor size was 2.9 cm (range: 0 to 8.5 cm) in greatest dimension. By AJCC 7th ed. T stage criteria, patients were classified as follows: 12 (4.2%) ypT0, 32 (11.1%) ypT1, 64 (22.1%) ypT2, and 181 (62.6%) ypT3 patients. By AJCC 8th ed. T stage criteria, the patients were classified as follows: 12 (4.2%) ypT0, 74 (25.6%) ypT1 (6 ypT1a, 1 ypT1b, 67 ypT1c), 161 (55.7%) ypT2, and 42 (14.5%) ypT3 patients (Table 3). No patients with ypT4 tumors underwent resection.

The 32 ypT1 tumors by 7th ed. criteria were reclassified to the following T stages by 8th ed. criteria: 30 ypT1, 1 ypT2, 1 ypT3. The 64 ypT2 tumors by 7th ed. criteria were reclassified as follows: 46 ypT2 and 18 ypT3. The 181 ypT3 tumors by 7th ed. criteria were reclassified as follows: 44 ypT1, 114 ypT2, and 23 ypT3. Overall, the stage increased in 20 patients (6.9%). 18 of these patients were 7th ed. ypT2 and 2 patients were ypT1. The stage decreased in 158 patients (54.6%). All downstaged tumors were classified as ypT3 using 7th ed. criteria

Table 3
T and N stages of patients based on 7th and 8th edition AJCC stage criteria.

	Number of patients (%)	
	AJCC 7th ed.	AJCC 8th ed.
T stage		
pT0	12 (4.2%)	12 (4.2%)
pT1	32 (11.1%)	74 (25.6%)
pT1a	N/A	6 (2.1%)
pT1b	N/A	1 (0.3%)
pT1c	N/A	67 (23.2%)
pT2	64 (22.1%)	161 (55.7%)
pT3	181 (62.6%)	42 (14.5%)
pT4	0 (0%)	0 (0%)
N stage		
pN0	182 (63.0%)	182 (63.0%)
pN1	107 (37.0%)	77 (26.7%)
pN2	N/A	30 (10.4%)

and had a lower stage by sized-based 8th ed. criteria.

The mean number of lymph nodes examined was 27 (range: 4 to 85). By AJCC 7th ed. N stage criteria, 182 patients (63.0%) were ypN0 and 107 patients (37.0%) were ypN1. By 8th ed. N stage criteria, 77 (26.7%) of patients were ypN1 and 30 patients (10.4%) were ypN2 (Table 3). Higher 7th ed. and 8th ed. T stage correlated significantly with lymph node positivity ($p < 0.001$ and $p = 0.04$, respectively) (Table 4).

3.3. Survival data

The mean follow-up time during the study was 39.0 months (range: 3.2 to 122.3 months). During the follow-up period, two of the patients with ypT0 disease developed disease recurrence and died of disease. One other patient with ypT0 disease died during the study of an unrelated cause but did not develop disease recurrence. The five-year overall survival (OS) rates by 7th ed. T stage were 32.7%, 36.1%, and 26.7% and by 8th ed. T stage they were 26.6%, 32.1%, and 25.9% for ypT1, ypT2, and ypT3, respectively. Kaplan-Meier survival curves including all patients stratified by 7th and 8th ed. AJCC T stage are shown in Fig. 1. 7th ed. T stage significantly correlated with OS ($p = 0.048$), while 8th ed. T stage did not correlate with OS ($p = 0.13$). In patients who were lymph node negative (ypN0) ($n = 182$ patients), neither the 7th ed. or 8th ed. T stages significantly correlated with patient OS ($p = 0.065$ and 0.26, respectively) (Fig. 2). The 5-year overall survival rates for ypN0 patients by 7th edition T stage were 39.6%, 40.8%, 25.7% and by 8th ed. T stage were 30.5%, 35.0%, and 28.7% for stage ypT1, ypT2, and ypT3, respectively. Within the ypN0 group, 8 patients had fewer than 12 lymph nodes examined; since the lymph node count was not adequate in these patients, a separate survival analysis was also performed on the remaining 174 ypN0 patients with 12 or more lymph nodes examined. Among this group of patients, the same trend in overall survival was seen (7th ed. $p = 0.12$ and 8th ed. $p = 0.33$).

Table 4
Correlation between 7th and 8th edition T stage and lymph node status.

Stage	−LN	+LN	p-Value
7th ed. T stage			
pT0	12 (100%)	0 (0%)	< 0.001
pT1	25 (78%)	7 (22%)	
pT2	52 (81%)	12 (19%)	
pT3	93 (51%)	88 (49%)	
8th ed. T stage			
pT0	12 (100%)	0 (0%)	0.04
pT1	46 (62%)	28 (38%)	
pT2	101 (63%)	60 (37%)	
pT3	23 (55%)	19 (45%)	

7th and 8th ed. T stage correlated significantly with progression free survival ($p = 0.03$ and $p = 0.01$, respectively). In ypN0 patients, there was no significant difference in PFS between T stage groups by either 7th or 8th ed. criteria ($p = 0.06$ and $p = 0.08$, respectively).

AJCC 7th ed. N stage correlated significantly with OS ($p = 0.004$). AJCC 8th ed. N stage also correlated significantly with patient OS ($p = 0.0002$) (Fig. 3). Including only patients with twelve or more lymph nodes ($n = 281$), AJCC 7th ed. N stage correlated significantly with patient OS ($p = 0.003$) and AJCC 8th ed. N stage also correlated significantly with patient OS ($p = 0.0002$).

4. Discussion

Patients with resectable and borderline resectable PDAC are increasingly treated with neoadjuvant chemotherapy and radiation therapy [14]. Neoadjuvant therapy causes numerous histologic changes which have been previously described. In most cases that show treatment effect, the tumor is primarily composed of fibrous stroma with interspersed single or small groups of tumor cells within the tumor bed. The tumor stroma can vary from loose and paucicellular to dense and fibrotic to cellular stroma with plump fibroblasts. This stroma can be quite difficult to grossly or microscopically distinguish from the surrounding atrophic, fibrotic background pancreas [15]. These changes can complicate assessment of the specimen and make measurement of tumor size more challenging than in cases resected without neoadjuvant therapy (treatment naïve tumors).

The change to entirely size-based staging criteria for resectable PDACs raises the importance of accurate measurement of tumor size. Many of the prior studies which focused on the prognostic utility of tumor size did not clearly report how tumor size was measured [6,8]. Presumably, much of the data in these studies is based on gross tumor size with some level of microscopic correlation. Currently, many institutions also likely rely on gross tumor size measurement owing to its simplicity. However, with tumor size measurement taking on a greater importance in staging, the optimal method of size measurement should be established for both untreated and treated tumors. Because of the unique challenges of measuring tumor size in patients with neoadjuvant therapy, the staging system should be validated separately for this group of patients. The goal of this study was to determine if the AJCC 8th edition T stage criteria correlate with prognosis in patients with neoadjuvant treated PDAC using gross tumor size.

We show that AJCC 7th ed. T stage significantly correlates with survival while the 8th ed. T stage (based on gross tumor size) does not correlate with overall survival in the same group of patients.

The same trend in overall survival is seen in patients without lymph node metastasis (ypN0 patients). 7th and 8th ed. T stage using gross tumor size correlated significantly with progression free survival ($p = 0.03$ and $p = 0.01$, respectively). Both 7th and 8th ed. T stage correlate significantly with lymph node status, with the 7th ed. T stage showing stronger correlation. Further, we show that lymph node status correlated significantly with prognosis by 7th and 8th edition criteria. The addition of an N2 group containing patients with four or more positive lymph nodes increased the prognostic significance of the 8th ed. N criteria compared to the 7th ed. criteria ($p = 0.004$ vs. $p = 0.0002$) and the ypN2 group separated well from the ypN1 group on the Kaplan-Meier survival curve. In summary, based on our data, changes to the N stages provide better prognostic stratification, while the 7th ed. criteria outperform the 8th ed. T stage criteria in predicting patient prognosis, when using gross tumor size measurements.

We also note the recent study by Chatterjee and colleagues, who showed prognostic significance of the 8th ed. criteria using a mapped approach that allowed for correlation between gross and microscopic tumor size [12]. This method appears to perform better than the approach based on gross tumor size used in our study. The major limitation of our approach is that for larger tumors it is impossible to utilize microscopic correlation to measure tumor size due to lack of a

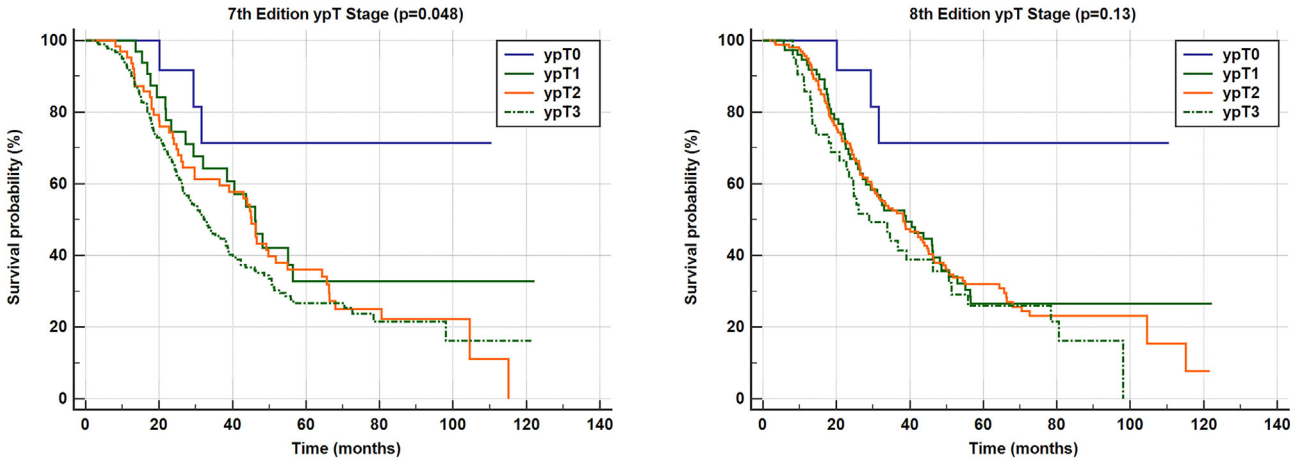

Fig. 1. Overall survival of all patients by 7th edition and 8th edition AJCC ypT stage.

standardized grossing protocol during our study period. Microscopic correlation was possible for cases in which the entire residual tumor was present on one slide, however this group made up a very small proportion of our cases. Our results, taken in association with those of Chatterjee and colleagues, suggest that a more labor-intensive approach to measuring tumor size is necessary to provide prognostically significant T staging in the neoadjuvant setting, and as such our institution has currently adopted a mapped grossing protocol.

Our findings also raise the question of whether tumor size is truly a prognostic factor in tumors with prior neoadjuvant therapy. In treatment naïve tumors, greatest tumor dimension is likely a good indicator of the level of progression of the tumor. However, tumor size in neoadjuvant treated cases is more complex and depends on several variables including level of tumor progression, overall treatment response, and heterogeneity of treatment response (distribution of residual tumor cells). A tumor with marked treatment response can have rare tumor cells distributed sparsely throughout a large tumor bed (and a large tumor size), whereas a tumor with a poor treatment response could have all residual tumor cells focused in a small area of the original tumor bed (and a small tumor size). Furthermore, it has been previously noted that portions of the tumor that are outside of the pancreas, particularly in the duodenal wall, may respond more poorly to neoadjuvant therapy [16].

Other methods of measuring tumor size have recently also been investigated including measuring the largest dimension of a single microscopic focus and the average size of all microscopic foci. The largest tumor deposit method has been shown in one study to be superior to using gross size alone. The benefit of this method is that it may not require a more labor intensive mapped gross technique; however, this method would require further assessment. Furthermore, some authors have suggested that a residual tumor index (% residual tumor x tumor size) may provide better prognostic stratification than tumor size alone [17]. At this time, the method of correlating gross and microscopic measurements has performed best [12,18]. However, other methods of tumor size measurement in the neoadjuvant setting deserve further study. Several methods for mapped grossing techniques have been described. Each method has benefits and downsides; from the perspective of measuring tumor size, the tumor should be serially sectioned and well sampled for microscopic examination. One recommendation is to entirely submit tumors < 3 cm and extensively sample those larger than 3 cm [16,19]. The levels should be numbered and submitted in order so that at the time of microscopic examination the greatest tumor dimension can be determined with microscopic correlation.

In conclusion, we show that the use of gross tumor size alone is inadequate for staging of neoadjuvant treated PDAC using the AJCC 8th edition criteria because it lacks prognostic significance. The 7th edition T stage criteria perform better than the 8th edition criteria using gross size measurements. At this time, the optimal method for size measurement is not entirely clear and further studies are necessary to address this question. Based on the current evidence, it appears that use of a mapped grossing approach which allows for correlation of gross and microscopic findings is necessary for accurate T staging of neoadjuvant treated PDAC.

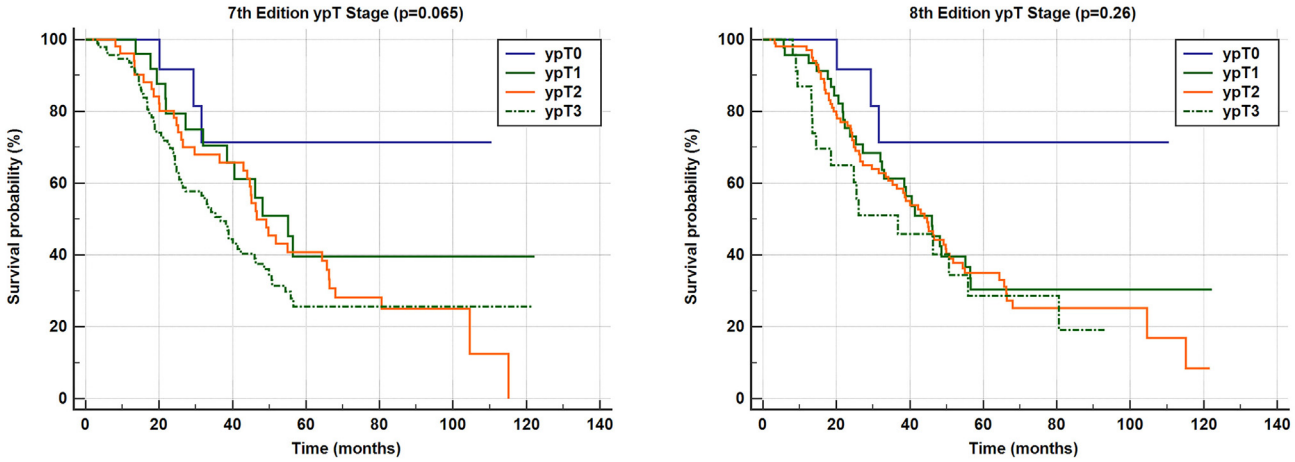

Fig. 2. Overall survival of lymph node negative patients by 7th edition and 8th edition AJCC ypT stage.

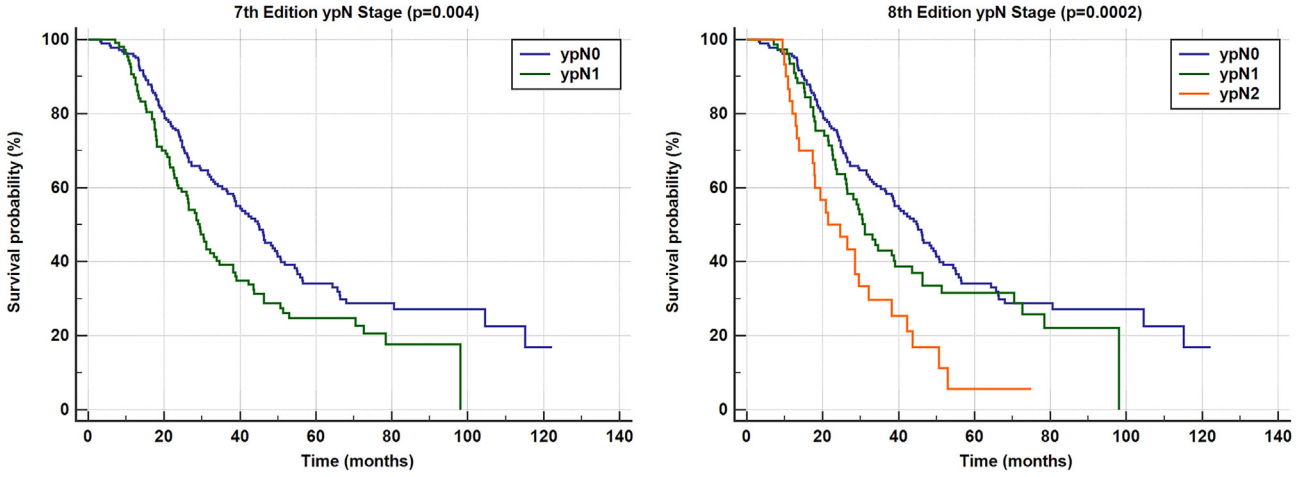

Fig. 3. Overall survival by 7th edition and 8th edition AJCC ypN stage.

Author contributions

Daniel Rowan contributed to data collection, data analysis, and writing and review of the manuscript. Christopher P. Hartley contributed to data analysis and review of the manuscript. Mohammed Aldakkak contributed to data collection, data analysis, and review of the manuscript. Kathleen K. Christians, Douglas B. Evans, and Susan Tsai contributed to data collection and review of the manuscript. Catherine E. Hagen contributed to design of the research study, data analysis, and writing and review of the manuscript.

Declaration of competing interest

None.

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