Clinics in Surgery

Research Article
Published: 09 Nov, 2018

Validation and Proposal for Refining the AJCC 8th Edition Staging System for Duodenal Adenocarcinoma

Sarang Hong, Ki Byung Song, Young-Joo Lee, Kwang-Min Park, Dae Wook Hwang, Jae Hoon Lee, Sang Hyun Shin, Jaewoo Kwon, Chung Hyeun Ma, Seunghyun Hwang, Guisuk Park, Yejong Park, Seung Jae Lee and Song Cheol Kim*

Department of Surgery, Division of Hepatobiliary and Pancreatic Surgery, University of Ulsan College of Medicine and Asan Medical Center, South Korea

Abstract

Background: Studies focusing on Duodenal Adenocarcinoma (DAC) are scarce and the clinicopathological features, patient characteristics, and survival factors of DAC are unknown. The 8th edition of the AJCC staging system for DAC incorporated the change focusing on positive Lymph Node (LN) numbers. We compared the classification systems in the 7th and 8th editions, and evaluated the clinicopathological features of and survival factors for DAC.

Methods: One hundred thirty-five DAC patients undergoing operations at As an Medical Center from 2000 to 2016 were restaged according to the AJCC 8th edition.

Results: One hundred and five patients underwent potentially curative resection and 30 underwent palliative surgery. In patients undergoing potentially curative resection, the median overall and disease-free survival were 89.5 and 52.1 months, respectively. The recurrence rate was 40.0%, with the liver being the most common site of metastasis. Although the new staging system for DAC could predict the prognosis satisfactorily, there is no other major improvement. A multivariate analysis revealed LN metastasis and T4 stage were the survival factors.

Conclusion: The AJCC 8th edition staging system has the appropriate ability to predict prognosis in DAC patients. However, the survival was mainly related to the T4 stage and the presence of LN metastasis. The simpler staging system emphasizing on the T4 stage and LN metastasis is recommended.

Keywords: Duodenal adenocarcinoma; Lymph node metastasis; T4 stage

OPEN ACCESS

Correspondence:
Ki Byung Song, Department of Surgery, Division of Hepatobiliary and Pancreatic Surgery, University of Ulsan College of Medicine and Asan Medical Center, Seoul, South Korea, Tel: 82-2-3010-1520; Fax: 82-2-3010-670; E-mail: mtsong21c@amc.seoul.kr

Received Date: *09 Oct 2018*
Accepted Date: *06 Nov 2018*
Published Date: *09 Nov 2018*

Citation:
Hong S, Song KB, Lee Y-J, Park K-M, Hwang DW, Lee JH, et al. Validation and Proposal for Refining the AJCC 8th Edition Staging System for Duodenal Adenocarcinoma. Clin Surg. 2018; 3: 2209.

Introduction

Small bowel cancer is a rare disease accounting for ≤ 5% of gastrointestinal cancers [1]. Although the duodenum is most frequently involved, Duodenal Adenocarcinoma (DAC) is rare and studies focusing on DAC are scarce. The clinicopathological features, patient characteristics, and survival factors of the disease are therefore not well known.

Lymph Node (LN) metastasis, Positive LN (PLN) number, T3 or T4 stage, and a positive resection margin are the prognostic factors for DAC and, particularly, LN metastasis has been reported as the main factor [2-6].

The American Joint Committee on Cancer (AJCC) 8th edition (most recent AJCC cancer staging manual), which published in 2016, included some notable modifications for DAC. The major modification is a new definition for N classification, with three positive LN were included in the N2 stage rather than in the N1 stage. In the 8th edition, the N-stage classification consisted of the following definitions: N0=node negative, N1 (1-2 positive regional LN), and N2 (≥ 3 positive regional LN). Because stages IIIA and IIIB are defined by N status, the modification resulted in a different classification of stage III. We aimed to compare the AJCC 7th and 8th edition classification systems, and evaluate the clinicopathological features, and survival factors of DAC.

Material and Methods

Data acquisition and study population

We conducted a retrospective medical record review of all patients with DAC. A total of 135 patients who underwent operation - either curative or palliative - at As an Medical Center from 2000 to 2016 were included. Patient characteristics and clinical, operative, and pathological data

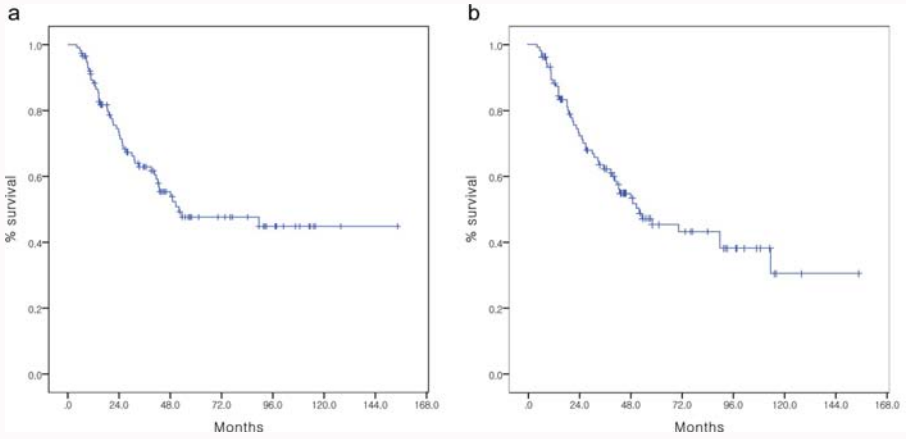

Figure 1: Overall survival and Disease free survival of patients with duodenal adenocarcinoma.

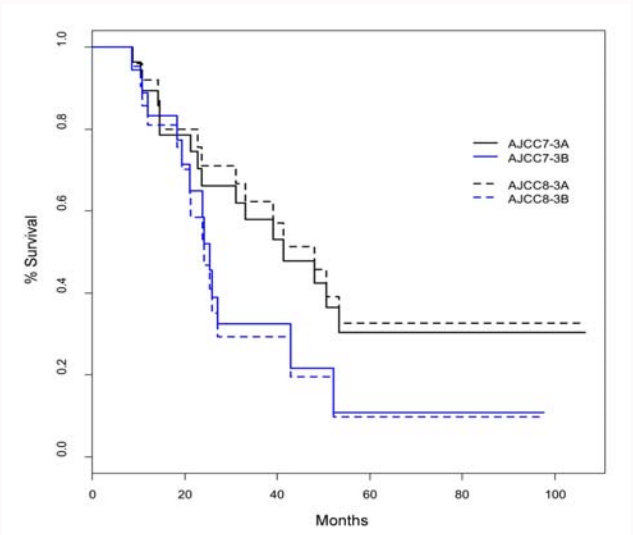

Figure 2: Survival curve for stage IIIA and IIIB group of both AJCC 7th and 8th systems.

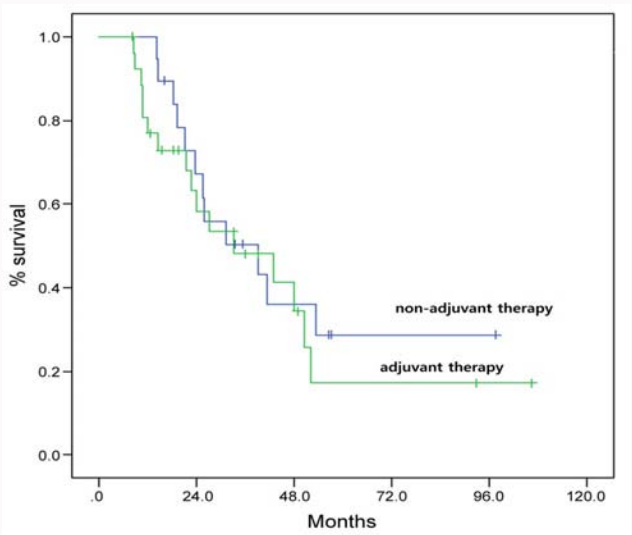

Figure 3: Survival curves for adjuvant and non-adjuvant therapy groups.

were retrieved.

Statistical analysis

All patients were staged according to both AJCC 7th and 8th edition guidelines. Disease-free Survival (DFS) and Overall Survival (OS) rates were estimated using the Kaplan-Meier method and compared using the log-rank test. Univariate and multivariate analyses were performed using the Cox proportional hazards regression model. A concordance index (c-index) was calculated to evaluate the discriminatory power of both staging systems. *P* values of <0.05 were considered statistically significant. Pathological review was performed by pathologists.

Result

We analyzed the data of 135 patients who underwent surgery for DAC from 2000 to 2016. There were 90 men and 45 women with a median age of 60 (range 27 to 84) years. The most common presenting symptom was abdominal pain (33.3%), including epigastric and flank pain, followed by dyspepsia (19.3%) and jaundice (10.4%). DAC was also incidentally discovered during regular checkup (15.6%).

Of the 135 patients, 30 were performed palliative resection due to liver metastasis, seeding, and locally advanced tumors. All patients with unresectable disease underwent bypass procedures consisting of gastrojejunostomy or duodenojejunostomy and palliative pancreatic resection with metastasectomy. The remaining 105 patients underwent potentially curative surgery, including gastrectomy (distal or subtotal), and pancreatectomy [Pancreaticoduodenectomy (PD), Pylorus-preserving Pancreaticoduodenectomy (PPPD), Subtotal Stomach Preserving Pancreaticoduodenectomy (SSPPD), or Total Pancreatectomy (TP)] and one patient underwent segmental duodenal resection.

The median tumor diameter was 3.9 cm and DAC mostly occurred at the second portion of the duodenum (71%). At least six LN were identified and examined in 98 patients (92.5%). The median LN number obtained was 16 and the median PLN number was 2. Of the 105 potentially curative resections, 101 resections (96.2%) were histopathologically confirmed as R0 and 4 (3.8%) as R1.

In 2008, there was an abrupt increase in patients undergoing surgery: 113 patients (83.7%) underwent surgery after 2008 (late period). Of the 26 stage-I patients, 24 (92.3%) underwent surgery after 2008. Of the 21 incidentally diagnosed asymptomatic patients, 20 (95.2%) were diagnosed and underwent surgery after 2008. However,

Table 1: Cox proportional hazards model evaluating the impact of PLN on survival.

	HR (95% CI)	P value
PLN=1 *vs.* 0	2.908 (1.021-8.281)	0.046
PLN=2 *vs.* 1	1.229 (0.400-3.777)	0.718
PLN=3 *vs.* 2	3.143 (0.637-15.494)	0.159
PLN=>4 *vs.* 3	0.460(0.101-2.101)	0.316

the tumor size (4.8 cm *vs.* 3.8 cm, p=0.949) and median survival (21 months *vs.* 43 months, p=0.197) did not differ between periods.

All 135 patients were staged according to both AJCC 7th and 8th staging systems. Reclassification of patients was exactly the same for stage I, IIA, IIB, and IV. However, since the N1 and N2 definition differed from the 7th edition, three patients under the AJCC 7th edition classification were upgraded from stage IIIA to IIIB under the new system.

105 out of 135 patients underwent potentially curative surgery. The median OS period for the 105 patients was 89.5 months, with 5-year and 10-year OS rates of 53.1% and 49.9%, respectively. 42 of the 105 patients (40.0%) had recurrence during median follow up time of 36.3 months. The median time to recurrence after operation was 7 months. Distant metastases occurred in 35 (83.3%) patients, loco-regional recurrence occurred in the remaining 7 (16.7%) patients. The liver was the most common site of distant metastasis, followed by the lung and peritoneum. The median DFS was 52.1 months, and the 5-year and 10-year DFS rates were 45.3% and 30.5%, respectively (Figure 1). The median OS for patients undergoing palliative surgery (n=30) was 9.7 months and the 5-year survival rate was 3.3%. The curative resection group had a significantly longer survival period than the palliative resection group (p<0.001). The median OS of R1 patients was shorter than that of R0 patients, but did not reach statistical significance (p=0.182). Staging using both systems resulted in exactly the same survival discrimination except for stage-III patients. The N1 stage under the 7th edition includes three PLN, whereas in the 8th edition, three PLN belong to the N2 stage. Patients in stage IIIA under the 7th edition showed a slightly lower survival rate than patients in stage IIIA under the 8th edition. The median OS for stage IIIA and IIIB under the 7th edition were 41 and 25 months, respectively, and 48 and 24 months under the 8th edition. The median survival was 39 months for N1 and 24 months for N2 according to the 7th edition, whereas the median survival was 41 months for N1 and 24 months for N2 according to the 8th edition. There is no difference in the median survival of stage-IIIB patients between the staging systems, but the median survival of stage-IIIA patients is slightly increased under the 8th edition. The c-index for the 8th edition was 0.772, similar to that for the 7th edition (0.768); this confirmed the lack of discriminatory power between two staging system editions (Figure 2).

The current AJCC N stage is divided by PLN number. Stratified analysis was performed to demonstrate the impact of PLN number (Table 1). In comparison between mortality risk and PLN number, the risk significantly increases when LN metastasis occurs regardless of PLN number (PLN=1 *vs.* 0, HR 2.908, p=0.046).

Tumors were divided into two groups according to size: <4 cm and ≥ 4 cm. The median survival of patients with a tumor size <4 cm was too long to reach to median survival rates of 50%, whereas that of patients with a tumor ≥ 4 cm was 33.1 months (p=0.064).

The median survival with a tumor size <4 cm in the LN metastasis-positive group was 48months, whereas that with a tumor size ≥ 4 cm was 23.8 months (p=0.036). The median survival

Table 2: Univariate and multivariate analyses for factors associated with overall survival.

Factors	No. of patients	Univariate (P)	Relative risk (95% CI)	Multivariate (P)
Age (years)				
≤ 70	80	0.113		
> 70	26			
Gender				
Male	72	0.045		
Female	34			
Tumor size (cm)				
< 4	61	0.064		
≥ 4	39			
T stage				
T1 + T2 + T3	58	0.002	0.920-4.203	0.048
T4	48			
Lymph node metastasis				
Absent	59	<0.001	1.145-6.862	0.002
Present	46			
Differentiation				
Well/moderate	95	0.785		
Poor	8			
Adjuvant therapy				
Yes	34	0.035		
No	72			

with smaller-sized and large-sized tumors in the LN metastasis-negative group was not significantly different (p=0.741). Tumor size may have an influence on OS when LN metastasis is present. Thirty four patients received adjuvant therapy and about 58.8% of them received 5-flourouracil (5-FU) based chemotherapy. Patients who did not receive adjuvant therapy had a longer median survival than those who received adjuvant therapy (NR *vs.* 42.9 months, p=0.023). Of 46 stage-III patients, 27 patients received adjuvant therapy and 19 did not. The median OS of the two groups were 33.1 months and 39.1 months, respectively (p=0.534) (Figure 3).

Multivariate analysis showed the significant influence of T4 stage (p=0.048) and LN metastasis (p=0.002) on OS (Table 2).

Discussion

DAC is an uncommon disease, constituting <0.5% of all gastrointestinal cancers [7]. Therefore, clinicopathological features, patient characteristics, and survival factors of the disease are poorly understood.

In this study, we analyzed 135 patients with DAC at a single high-volume center. We aimed to examine the disease characteristics and to compare the AJCC 7th and 8th edition staging systems so as to evaluate the factors that impact survival and to ascertain the relative significance of nodal classification in predicting survival.

Several previous studies have reported on the survival factors of DAC. Most of them suggested LN invasion, T3 or T4 stage, and a positive resection margin as negative factors for OS of DAC [2-5,8-10].

Complete resection (R0) of the primary tumor with locoregional LN resection is mandatory, but it is not always feasible in patients with locally advanced tumors. There is general agreement that patients with resectable DAC achieve better survival times than those with unresectable tumors [2]. In the present study, 30 patients who underwent palliative surgery had a significantly shorter survival than those who underwent potentially curative surgery (p<0.001). Among the potentially curative surgery group, more patients with R1 resection had systemic recurrence than R0 patients, 100% *vs.* 82.5%, and patients with R1 resection had larger tumors than R0 patients, 6.3 cm *vs.* 3.7 cm. Also, although not statistically significant, there was a definite difference in the median survival between the R0 and R1 resection group (NR *vs.* 22.8 months, p=0.182).

For DAC, a Whipple resection has been recommended as first-choice procedure. There were two trials focusing on the difference between resection types: classic Whipple resection and pylorus-preserving technique. Both studies reported that there was no significant difference in the OS, tumor recurrence, or quality of life; thus, the two procedures were equally effective in periampullary carcinoma treatment [11,12]. In our study, 47 patients underwent PPPD and 50 PD or SSPPD. When comparing PPPD and PD or SSPPD groups, there were no significant differences in the recurrence rate (40% *vs.* 46%, p=0.584) and in the positive resection margin (2.1% *vs.* 6%, p=0.343). There was a significant difference in the OS (NR *vs.* 41.4 months, p=0.001) because the data did not take into account other risk factors. Tumor size was larger for PD or SSPPD than for PPPD (4.5 cm *vs.* 3.1 cm). There were more stage-III patients for PD or SSPPD than for PPPD (52.0% *vs.* 31.9%). It was observed that operation type did not prove to be a significant determinant of outcome, if we obtain a safety resection margin. We need further evaluation to prove a resection type as the survival factor of the patients with DAC in the future.

Adjuvant therapy has not shown proven benefits following curative resection in patients with DAC [6,13]. Although data are limited guiding adjuvant therapy options, 5FU-based chemotherapy is typically offered to high risk patients of recurrence, such as stage-III patients in present study. Out of 46 stage-III patients, 27 patients received adjuvant therapy. We compared this group with those who did not receive for the analysis of the overall prognosis. The median OS of the two groups were 33.1 months and 39.1 months, respectively (p=0.534). Also, in multivariate analysis, adjuvant therapy had no prognostic significance for survival. Therefore, the effectiveness of adjuvant therapy cannot be concluded in this study. We need further evaluation to prove effectiveness of adjuvant therapy in the future.

The proportion of the population diagnosed with duodenal cancer is increasing in Korea because of improvements in the health-care system and the nationwide routine checkup through esophagogastroduodenoscopy. We analyzed the clinicopathological features of DAC from the early (2000-2007) to the late (2008-2016) period. There was an increase in patient numbers who were incidentally diagnosed with asymptomatic DAC (4.8% *vs.* 95.2%). Also tumor size slightly decreased (4.8 cm *vs.* 3.8 cm), and median survival increased (21 months *vs.* 43 months, p=0.197). Of the total 135 patients, 110 patients presented various symptoms at the time of diagnosis. The median OS of symptomatic and asymptomatic patients were 31.1 months and 53.4 months, respectively (p=0.037). It can be concluded that early detection of the disease by the routine checkup when patients are still asymptomatic is important to begin appropriate treatment.

The major difference between the 7th and the 8th staging system is the nodal status: the classification of three PLN is upgraded from N1 stage to N2 stage; stage-IIIA patients under the AJCC 7th edition should be shifted up to IIIB under the AJCC 8th edition.

Although the median OS of stage IIIA under the 8th edition is higher than that of stage IIIA under the 7th edition, and the median OS of stage IIIB under the 8th edition is lower than that of stage IIIB under the 7th edition, the difference between survival and c-index is subtle (0.768 *vs.* 0.772), showing no significant discriminatory power.

Previous studies demonstrated that T3 or T4 stage was a significant prognostic predictor [2,10]. T stage is divided according to tumor depth and T4 stage is defined as serosal invasion whereas T3 stage is defined as without serosal perforation. When comparing T3 and T4 in our study, the median OS were NR and 33.1 months (p=0.043) and tumor sizes were 3.4 cm and 5.2 cm, respectively (p=0.036). Also, T4 stage was a statistically significant prognostic factor of DAC in univariate and multivariate analyses. In the AJCC 8th edition staging system, T stage for pancreatic cancer emphasizes on tumor size. On the other hand, T stage for duodenal cancer and ampulla of Vater cancer does not include tumor size. In the present study, although it was not statistically significant (p=0.064), patients with smaller-sized tumors had longer median OS than patients with larger-sized tumors. Also, when LN metastasis is present, the median survival with a tumor size <4 cm was longer than that with a tumor size ≥ 4 cm (48 months, *vs.* 24 months, p=0.036). Larger tumors might have been present longer and have had more chances of metastasizing or invading adjacent structures. Further study is recommended to evaluate the importance of tumor size to include this factor in T stage.

LN metastasis has been associated with poor prognosis by previous investigators [2-4]. Sarela et al. demonstrated that nodal metastasis was an independently significant prognostic factor especially when LN is thoroughly extirpated (≥ 15) [8]. In our study, LN metastasis was a statistically significant prognostic factor in univariate and multivariate analyses. It was definitely ascertained that survival is related to LN metastasis. When separating LN metastasis into subdivision according to PLN number and comparing the risk of each subdivision, it was found that PLN number (1 *vs.* 2 *vs.* 3) did not have an influence on survival. Rather, the mortality risk was more significant when LN metastasis is present regardless of PLN number (PLN 0 *vs.* 1, p=0.046).

This data show that DAC survival is mainly determined by T4 stage and the presence of LN metastasis.

It is recommended for future studies to develop a new staging system that reflects the significance of the T4 stage and nodal metastasis in multicenter trials.

Conclusion

In conclusion, although the AJCC 8th edition staging system has the ability to predict DAC survival, it bears no difference from the 7th edition staging system. This study shows that survival is mainly related to the T4 stage and the presence of LN metastasis rather than positive LN number. The simpler staging system emphasizing the T4 stage and LN metastasis is therefore recommended.

References

1. Neugut AI, Jacobson JS, Suh S, Mukherjee R, Arber N. The epidemiology of cancer of the small bowel. Cancer Epidemiol Biomarkers Prev. 1998;7(3):243-51.
2. Bakaeen FG, Murr MM, Sarr MG, Thompson GB, Farnell MB, Nagorney DM, et al. What prognostic factors are important in duodenal adenocarcinoma? Arch Surg. 2000;135(6):635-41.
3. Liang TJ, Wang BW, Liu SI, Chou NH, Tsai CC, Chen IS, et al. Number of involved lymph nodes is important in the prediction of prognosis for primary duodenal adenocarcinoma. J Chin Med Assoc. 2012;75(11):573-80.
4. Lee HG, You DD, Paik KY, Heo JS, Choi SH, Choi DW. Prognostic factors for primary duodenal adenocarcinoma. World J Surg. 2008;32(10):2246-52.
5. Lee SY, Lee JH, Hwang DW, Kim SC, Park KM, Lee YJ. Long-term outcomes in patients with duodenal adenocarcinoma. ANZ J Surg. 2014;84(12):970-5.
6. Halfdanarson TR, McWilliams RR, Donohue JH, Quevedo JF. A single-institution experience with 491 cases of small bowel adenocarcinoma. Am J Surg. 2010;199(6):797-803.
7. Yeo CJ, Sohn TA, Cameron JL, Hruban RH, Lillemoe KD, Pitt HA. Periampullary adenocarcinoma: analysis of 5-year survivors. Ann Surg. 1998;227(6):821-31.
8. Sarela AI, Brennan MF, Karpeh MS, Klimstra D, Conlon KC. Adenocarcinoma of the duodenum: importance of accurate lymph node staging and similarity in outcome to gastric cancer. Ann Surg Oncol. 2004;11(4):380-6.
9. Ryder NM, Ko CY, Hines OJ, Gloor B, Reber HA. Primary duodenal adenocarcinoma: a 40-year experience. Arch Surg. 2000;135(9):1070-4.
10. Kawahira H, Miura F, Saigo K, Matsunaga A, Natsume T, Akai T, et al. Survival predictors of patients with primary duodenal adenocarcinoma. Int Surg. 2011;96(2):111-6.
11. Seiler CA, Wagner M, Bachmann T, Redaelli CA, Schmied B, Uhl W, et al. Randomized clinical trial of pylorus-preserving duodenopancreatectomy versus classical Whipple resection-long term results. Br J Surg. 2005;92(5):547-56.
12. Tran KT, Smeenk HG, van Eijck CH, Kazemier G, Hop WC, Greve JW, et al. Pylorus preserving pancreaticoduodenectomy versus standard Whipple procedure: a prospective, randomized, multicenter analysis of 170 patients with pancreatic and periampullary tumors. Ann Surg. 2004;240(5):738-45.
13. Overman MJ, Kopetz S, Lin E, Abbruzzese JL, Wolff RA. Is there a role for adjuvant therapy in resected adenocarcinoma of the small intestine. Acta Oncol. 2010;49(4):474-9.