Research Article

Prognostic Factors and Clinical Characteristics of Patients with Primary Duodenal Adenocarcinoma: A Single-Center Experience from China

Qing-Long Jiang, Xiang-Hui Huang, Ying-Tai Chen, Jian-Wei Zhang, and Cheng-Feng Wang

Department of Abdominal Surgery, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China

Correspondence should be addressed to Cheng-Feng Wang; chengfengwang1962@163.com

Aim. To evaluate the clinical risk factors influencing overall survival of patients with duodenal adenocarcinoma after potentially curative resection. *Methods.* A series of 201 patients with primary duodenal adenocarcinoma who underwent surgery from 1999 to 2014 at Chinese Medical Academic Cancer Hospital were studied by retrospective chart review and subsequent telephone follow-up. *Results.* Resectional surgery was performed in 138 of the 201 patients to attempt curative treatment, while 63 patients were treated with palliative surgery. Median survival of patients who underwent resectional operation was 57 months, whereas that of patients who had palliative surgery was shorter, 7 months ($p < 0.001$). For patients who underwent radical resection, the overall 1-, 3-, and 5-year survival rates were 87.3, 59.1, and 44.1%, respectively. Multivariate Cox regression analysis revealed that lymph node metastasis (HR 31.76, 2.14 to 470.8; $p = 0.012$) and vascular invasion (HR 3.75, 1.24 to 11.38; $p = 0.020$) were independent prognostic factors negatively associated with survival in patients undergoing curative resection. There was no survival difference between the groups treated by the pancreaticoduodenectomy ($n = 20$) and limited resection ($n = 10$) for early-stage duodenal adenocarcinoma ($p = 0.704$). *Conclusions.* Duodenal adenocarcinoma is a rare disease. Curative resection is the best treatment for appropriate patients. Lymph node metastases and vascular invasion are negative prognostic factors.

1. Introduction

Although the incidence of duodenal cancer has been increasing, duodenal adenocarcinoma (DA) remains a rare malignancy. Its incidence is estimated at less than 0.5 per 100,000 individuals [1]. Surgical resection is the only potentially curative treatment [2]. However, given the low prevalence of this disease in the general population and the limited number of clinical studies, there is no consensus as to the most effective treatment strategy. Conflicting information exists on the required extent of resection of duodenal adenocarcinoma [3, 4]. Some have suggested pancreaticoduodenectomy for all duodenal adenocarcinoma patients, regardless of TNM (tumor-node-metastasis) stage and location, to ensure that there is a tumor-free (R0) margin and adequate regional

lymphadenectomy. Others have advocated the use of segmental resection for appropriate patients [3]. In the last decade, different studies have evaluated the correlations between clinical, pathological, and treatment variables in order to identify specific prognostic factors associated with survival [4–9]. Identifying the prognostic factors is of great significance for the comprehensive understanding of the characteristics of this disease and has an important guiding meaning for the disease prevention and treatment. So the aims of this study were to retrospectively evaluate the clinicopathologic features of patients with duodenal adenocarcinoma treated over a 16-year period at the National Cancer Center of China and to identify significant prognostic factors in patients who had been treated with potentially curative radical resection.

2. Patients and Methods

The medical records of all patients diagnosed with duodenal adenocarcinoma from January 1999 to January 2015 in the Cancer Hospital, Chinese Academy of Medical Science, Peking Union Medical College, were studied by retrospective chart review which was approved by our Institutional Review Board. The cancer diagnoses were confirmed by the microscopic pathology of biopsy specimens or resected masses. Patients with cancers other than primary duodenal adenocarcinoma were excluded.

Clinical data collected included patient age, sex, tumor location, type of operation, tumor size, grade, TNM stage, CEA level, lymph node metastasis, perineural invasion, vascular invasion, local recurrence and metastasis, and adjuvant therapy. TNM staging was according to the American Joint Committee on Cancer standards (AJCC, 7th edition). Follow-up information was obtained by telephone interviews and outpatient follow-up and was calculated by interquartile range. The primary outcome variable was overall survival defined as the period from date of surgery to date of death.

3. Statistical Analysis

Data were analyzed using SPSS software, version 14.0 (SPSS, Inc., Chicago, IL, USA). Survival analysis was performed according to the Kaplan–Meier method. Possible prognostic factors influencing survival for resected cases were first evaluated by univariate analysis (log-rank test). Only parameters that showed significance by univariate analysis were further analyzed by multivariate analysis (Cox proportional hazards test, method forward-conditional). Statistical significance was defined as a p value < 0.05.

4. Results

4.1. Patient Characteristics. A total of 201 patients with duodenal adenocarcinoma who had surgical treatment were studied retrospectively. The in-hospital mortality rate was 4.3% (6 of 138) among those who had resectional surgery, whereas it was 1.6% (1 of 63) for the patients who had less aggressive palliative surgery performed. Seven patients were lost to follow-up (4 from the aggressive therapy and 3 from the palliative treatment group). Thus, 187 of the 201 patients could be included in the long-term survival analyses. Of these 187, a potentially curative operation was performed on 128 (68%), and 59 (32%) were provided with palliative care (gastrojejunostomy or double bypass). The median age was 58 years (range: 23 to 79). Twenty-three patients required preoperative biliary drainage for severe jaundice. After surgical treatment, adjuvant chemoradiotherapy was administered to 62 (33%) of the 187 patients.

4.2. Tumor Characteristics. The median tumor size was 4 cm (range: 1 to 20 cm). Most patients' tumors were located in the D2 portion separate from the ampulla (84%) and had moderate differentiation (54%). For the resection surgery group, R0 resection (with surgical margins free of neoplasia) was achieved in all cases. On pathologic examination, 9

patients (7.0%) had T1, 25 (19.5%) T2, 36 (28.1%) T3, and 58 (45.3%) T4 tumors. The patients who qualified for resection surgery most frequently presented with stage III disease (stage I, 25%; stage II, 26%; stage III, 45%; stage IV, 0), whereas most of the patients who were treated with palliative care presented with stage IV disease (stage I, 0; stage II, 2%; stage III, 10%; stage IV, 88%). The TNM staging and pathological data are summarized in Table 1. The median number of lymph nodes resected was 13 and ranged from 1 to 54 for 121 resectional surgery patients (7 patients with limited resections had no lymph node specimens submitted for pathology).

4.3. Survival Analysis. The median follow-up was 20 (2 to 84) months. The overall survival of patients who underwent R0 resection was better than those who were treated with only palliative surgery for advanced disease at diagnosis (median survival time: 57 months versus 7 months, $p < 0.001$; see Figure 1). For patients who underwent resection operation, the overall 1-, 3-, and 5-year survival rates were 87.3, 59.1, and 44.1%, respectively. In univariate analysis, advanced tumor T stage, poor tumor differentiation, presence of lymph node metastasis, perineural invasion, vascular invasion, increased CEA level, higher TNM stage, and tumor metastasis were all associated with a poor prognosis (Table 2). But age, gender, BMI (body mass index), tumor size, tumor location, intraoperative transfusion, and adjuvant chemoradiotherapy were not associated with survival. The results of multivariate Cox regression analysis showed lymph node metastasis (HR 31.76, 2.14 to 470.8; $p = 0.012$) and vascular invasion (HR 3.75, 1.24 to 11.38; $p = 0.020$) were independent factors associated with poor overall survival in patients who had surgical resection (Table 2, Figure 2).

Interestingly, limited or segmental resections tended to be performed in patients with early-stage disease, and the Whipple procedure tended to be performed in the more advanced cases, but survival analysis to evaluate the effect of the two types of surgery in early-stage patients found no difference between the two techniques ($p = 0.704$) (Figure 3).

5. Discussion

Duodenal adenocarcinoma is a rare cancer, with an incidence of less than 0.5 per 100,000 individuals [1]. Surgical resection is the only potentially curative treatment for this malignancy. The published literature indicates that in patients with these tumors who undergo radical resection the 5-year survival rates range from 25 to 54% [2, 5–8]. In our study, the patients who were treated with radical surgery had a 5-year survival rate of 44.1%, similar to prior studies. Because of the low incidence and prevalence of this malignancy, few studies have been published, and the factors that influence survival remain obscure. Therefore, issues such as lymph node status, the type of surgical resection, and the role of adjuvant treatments in the prognosis of these patients remain controversial [9–14]. In the present chart review, the presence of positive lymph node metastases was the most important prognostic factor for a poor outcome in patients with duodenal adenocarcinoma. This is in agreement with

TABLE 1: The clinical and pathologic details for resected cases of duodenal adenocarcinoma.

Characteristics	Number of patients (%)
Gender	
Male	78 (60.9)
Female	50 (39.1)
Age	
≤60 years	72 (56.3)
>60 years	56 (43.7)
Body mass index, median (range)	
CEA level	
>5	17 (15.3)
≤5	94 (84.7)
Tumor location	
D1	5 (3.9)
D2	113 (88.3)
D3	9 (7.0)
D4	1 (0.8)
Surgery procedure	
Whipple	112 (87.5)
Segmental resection	16 (12.5)
T stage	
T1	9 (7.1)
T2	25 (19.5)
T3	36 (28.1)
T4	58 (45.3)
Tumor size	
>5 cm	27 (21.1)
≤5 cm	101 (78.9)
Differentiation	
High	24 (18.8)
Middle	60 (46.9)
Low	44 (34.3)
Vascular invasion	
Yes	29 (28.4)
No	73 (71.6)
Perineurial invasion	
Yes	22 (22.7)
No	75 (77.3)
Lymph node status	
Positive	49 (40.5)
Negative	72 (59.5)
Transfusion	
Yes	64 (50)
No	64 (50)
TNM stage (AJCC)	
I	30 (23.4)

TABLE 1: Continued.

Characteristics	Number of patients (%)
II	46 (36.0)
III	52 (40.6)
Recurrence and metastasis	
Yes	39 (30.7)
No	88 (69.3)
Adjuvant therapy	
Yes	48 (37.5)
No	80 (62.5)
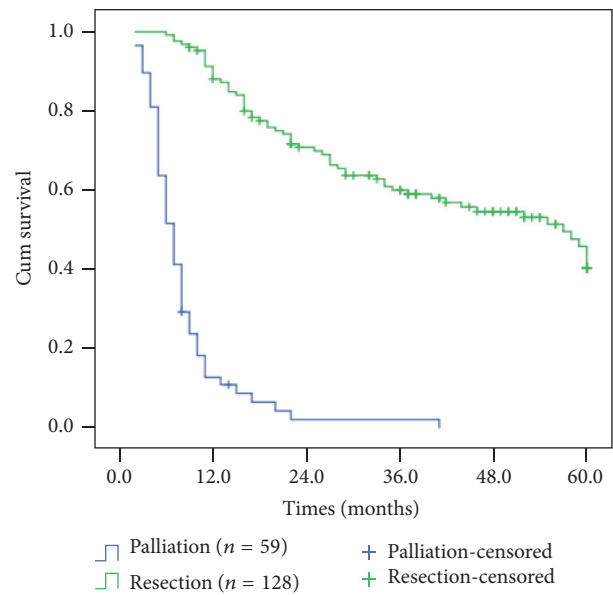
Number at risk						
Palliation	59	7	1	1	0	0
Resection	128	112	89	75	68	56

FIGURE 1: Overall survival after potentially curative resection compared with a palliative surgical procedure: the overall 1-, 3-, and 5-year survival rates were 87.3, 59.1, and 44.1% for patients who underwent resection operation, while being 12.8%, 2.2%, and 0 for palliation group. The median survival was 57 months versus 7 months. $p < 0.001$.

the study of Poultsides, who evaluated 122 duodenal adenocarcinoma patients treated with the Whipple procedure; they concluded that lymph node metastasis was the single independent prognostic factor associated with survival on multivariate Cox regression analysis. The 5-year survival of node-negative patients was 68% but only 17% for those who had four or more positive nodes [15]. Another study showed a 3-year survival rate of 87.5% for patients with node-negative patients and 21% for node-positive cases [8]. In contrast, Malleo et al. reported that the nodal status did not correlate with overall survival [16]. Other studies have reported that the ratio of positive lymph nodes to total number of lymph
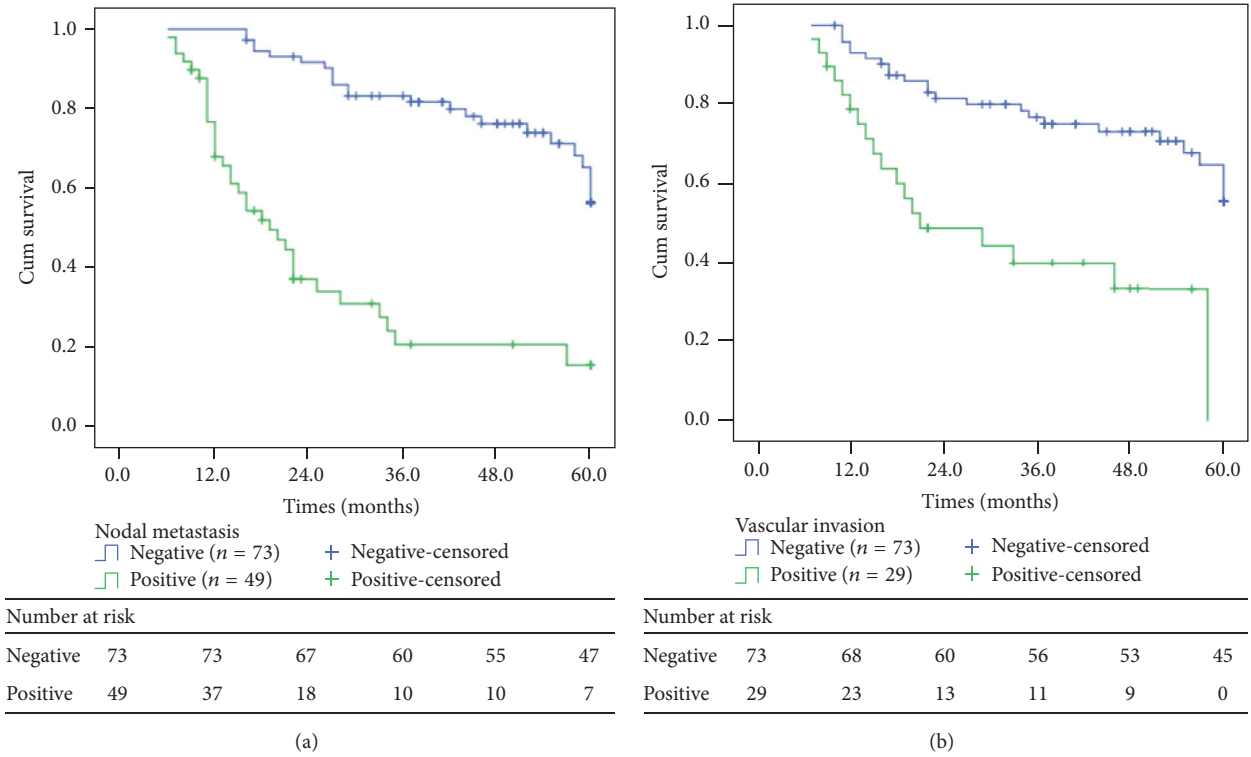
Number at risk

| Negative | 73 | 73 | 67 | 60 | 55 | 47 |
| Positive | 49 | 37 | 18 | 10 | 10 | 7 |

(a)

| Negative | 73 | 68 | 60 | 56 | 53 | 45 |
| Positive | 29 | 23 | 13 | 11 | 9 | 0 |

(b)

FIGURE 2: (a) Kaplan–Meyer survival curves comparing patients within the curative resection group by nodal status; (b) Kaplan–Meyer survival curves comparing patients within the curative resection group by vascular invasion.
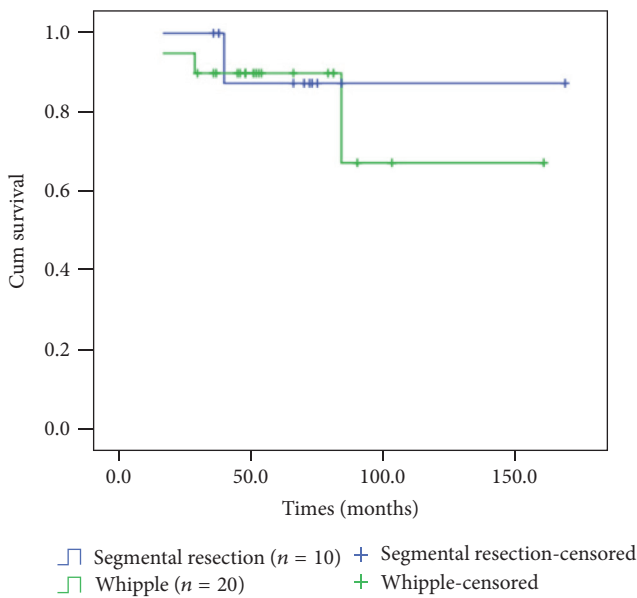

FIGURE 3: Kaplan–Meier survival curves for stage I patients undergoing Whipple procedure and segmental resection. $p = 0.704$.

node specimens resected is also a significant prognostic factor [15, 17]. The present data support the suggestion that a high positive lymph node ratio is associated with a poor prognosis ($p < 0.001$). However, definitive proof of a mechanistic association between nodal status and survival will require a larger-scale multicenter investigation.

Debates on the most appropriate surgical approach to duodenal cancers have lasted for years. Some authorities have argued that only the Whipple procedure ensures cancer-free surgical margins and appropriate regional lymph node resection. Alternatively, for some cases, especially distal or proximal duodenal adenocarcinoma, segmental resection might be an appropriate alternative. Bakaeen et al. [18] studied 50 patients treated with radical resection and 15 patients who had limited resection and found similar postoperative morbidity and overall similar outcomes. But significantly shorter length of hospital stay occurred in the limited resection group. Similarly, Tocchi et al. [13] found that patients who were treated with segmental resection had less postoperative morbidity and mortality, shorter length of hospital stay, and equivalent overall survival. According to those studies, when negative margins were attainable, segmental resection might be a better choice for duodenal adenocarcinoma patients. In the present study, a survival analysis was conducted to evaluate the effect of the choice of operation on the prognosis of early duodenal adenocarcinoma. The result showed there is no survival difference between segmental resection and the Whipple procedure for patients without advanced disease ($p = 0.704$). However, more high-quality, multicenter, large-sample randomized controlled trials are required to fully validate this conclusion.

TABLE 2: Results of the Cox regression to identify independent potential variables influencing overall survival of patients undergoing resection for duodenal adenocarcinoma.

Characteristics	Univariable analysis		Multivariable analysis	
	Hazard ratio	p value	Hazard ratio	p value
Age*	1.53 (0.92–2.54)	0.100		
Gender (male versus female)	1.56 (0.94–2.58)	0.087		
BMI*	0.80 (0.55–1.67)	0.246		
Tumor size*	0.56 (0.29–1.11)	0.098		
Tumor location*	0.84 (0.43–1.61)	0.589		
T stage*	1.84 (1.35–2.52)	<0.001	1.05 0.58–1.92	0.866
Differentiation*	0.79 (0.66–0.95)	0.013	0.84 0.65–1.10	0.210
Vascular invasion (yes versus no)	3.71 (1.94–7.08)	<0.001	3.75 1.24–11.39	0.020
Perineurial invasion (yes versus no)	2.19 (1.05–4.55)	0.036	0.49 0.16–1.49	0.211
Lymph node metastasis (yes versus no)	5.77 (3.32–10.02)	<0.001	31.76 2.14–470.8	0.012
TNM stage*	1.94 (1.49–2.52)	<0.001	0.51 0.18–1.45	0.207
CEA level (elevated versus normal)	2.09 (1.07–4.09)	0.032	1.26 0.41–3.88	0.689
Transfusion (yesversus no)	1.16 (0.70–1.93)	0.560		
Recurrence and metastasis (yes versus no)	4.66 (2.73–7.96)	<0.001	1.67 0.65–4.28	0.281
Adjuvant therapy (yes versus no)	1.25 (0.75–2.09)	0.389		

*Analyzed as continuous variable.

The roles of adjuvant chemotherapy and/or radiotherapy for duodenal adenocarcinoma after operation are not clear [19–21]. Previous studies have indicated that adjuvant chemoradiation provided improved local control after surgery but did not have overall survival benefit [10]. Aphase II prospective trial from M.D. Anderson Cancer Center showed encouraging results, with a response rate of nearly 50% when oxaliplatin and capecitabine combination therapy was employed [21]. In our retrospective study, adjuvant chemotherapy was not associated with improved overall survival ($p = 0.389$). Unfortunately, our data did not include the full details of adjuvant therapy. The role of adjuvant systemic chemotherapy certainly deserves further investigation.

6. Conclusion

Radical resection and the Whipple procedure (pancreaticoduodenectomy) if indicated provide the best chance of successful treatment for duodenal adenocarcinoma patients. Obviously, palliative surgery is reserved for cases where the disease is diagnosed at an advanced state and radical surgery would not confer any survival benefit. Lymph node metastases and vascular invasion at time of surgery are strongly associated with a negative prognosis. Therefore, adequate lymph node dissection is important for survival prediction and management. At the same time, our results support the notion that segmental small bowel resection is an acceptable and less traumatic alternative surgical procedure, which can be appropriate for a subset of patients with less advanced duodenal adenocarcinoma, when negative surgical margins can be achieved.

Competing Interests

The authors declare that they have no competing interests.

Authors' Contributions

C. F. Wang designed the study; Y. T. Chen, J. W. Zhang, and Q. L. Jiang performed the operation; Q. L. Jiang and X. H. Huang did the statistical analysis; Q. L. Jiang wrote the paper.

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