Surgical treatment and outcome for primary duodenal adenocarcinoma. Single center experience



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AIM: In this study, we aimed to evaluate patients who underwent curative surgical treatment for primary duodenal adenocarcinoma and to present our experience.

MATERIAL AND METHODS: Patients diagnosed with primary duodenal adenocarcinoma between 2006 and 2018 participated in the study. The demographic and clinical characteristics of the patients, details of the operation, pathological features of the tumors, short- and long-term follow-up results, and mean survival were evaluated retrospectively.

RESULTS: Nine patients with a mean age of 54.7 participated in the study. 55% of the patients were male. The most common presenting symptom was abdominal pain (n: 6; 67%). The most common tumor localization was D2-3 (n: 7; 78%), and the most common surgical operation was pancreaticoduodenectomy (n: 7; 78%). There were no intraoperative complications in any patient. The mean tumor diameter was 3.5 cm. The mean number of lymph nodes dissected was 8.3 and the mean number of metastatic lymph nodes was 2. The most common postoperative complication was pancreatic fistula (n: 3; 33%). The mean length of stay was 21.8 days. One patient developed septic shock and mortality happened within the 30-day period. The most common cause of unplanned admission to the hospital within 90 days was wound infection (n: 2; 22%). One patient developed local recurrence and two patients had systemic metastasis. We found an average survival of 40 months.

DISCUSSION: Pancreaticoduodenectomy is the most common approach in its curative surgery and it has a long survival despite the high postoperative complication rate. We recommend radical resection in the surgical treatment of primary duodenal adenocarcinoma.

KEY WORDS: Adenocarcinoma, Duodenum, Pancreaticoduodenectomy

Introduction

Despite the increased incidence of duodenal cancer, duodenal adenocarcinoma (DA) is a rare malignancy. The incidence is estimated to be less than 0.5 per 100,000 individuals ¹. Although duodenum is the most common site for adenocarcinoma in the small intestine, duodenal adenocarcinoma (DA) accounts for less than 1% of all gastrointestinal cancers ^{2,3}. Duodenal tumors have diagnostic difficulties because of their rarity, nonspecific signs and symptoms, and the fact that the duodenum is often overlooked during upper gastrointestinal endoscopy ^{4,5}.

Surgical resection is a potentially curative treatment ⁶. However, given the low prevalence of this disease in the general population and the limited number of clinical trials, there is no consensus on the most effective treatment strategy ⁵. In the literature, there are authors advocating the use of segmental resection for appropriate patients as well as those recommending pancreatoduo-denectomy for all duodenal adenocarcinoma patients, regardless of stage and location of TNM, to ensure that there is tumor-free (R0) margin and adequate regional lymphadenectomy ^{7,8}.

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In this study, we aimed to evaluate patients who underwent curative surgical treatment for primary duodenal adenocarcinoma and to present our experience.

Material and Method

Patients diagnosed as having duodenum adenocarcinoma, after the histopathological examination of the biopsy specimen taken by the endoscopic method in the General Surgery Clinic of Ercives University Faculty of Medicine (EUFoM) between 2006 and 2018 were included in the study. For inclusion in this study, a surgeon and pathologist had to agree that the duodenum was the primary tumor location. Patients with primary tumors arising from the bile duct, pancreas, or ampulla of Vater were excluded. Only primary duodenal adenocarcinomas that had been confirmed by pathological assessment were included. Patients with benign or malignant tumors other than adenocarcinoma were also excluded. A common database was created by examining patient files and hospital information system records. Using this database, patients' demographic characteristics, body mass indexes (BMI), comorbid diseases, American Society of Anesthesiologists (ASA) scores, neoadjuvant treatment status, preoperative CEA and Ca 19.9 levels tumor localizations, applied type of operation, duration of operation, mean blood loss, intraoperative complications, additional organ resections, tumor diameters, tumor grade, pathological stages, number of dissected metastatic and total lymph nodes (LN), postoperative hospital stay, postoperative complications, reoperations, perioperative mortality, unplanned unplanned re-admission to hospital within 90 days, whether local recurrence or systemic metastasis developed, survival time and current clinical status were evaluated retrospectively.

The location of the tumor was designated based on it being in the first portion of the duodenum (D1), second portion (D2), third portion (D3), or fourth portion (D4). If the tumor involves two or more portions of the duodenum, each portion of duodenum is expressed together.

Patients with primary duodenal carcinoma were discussed at a weekly multidisciplinary disease management conference attended by gastrointestinal and hepatopancreatobiliary surgeons, medical oncologists, radiologists, gastroenterologists and pathologists. The decision of neoadjuvant treatment was made by the primary surgeon and consensus at the multidisciplinary conference. The reasoning for neoadjuvant therapy was an attempt to downstage the disease to avoid a radical resection, if possible. Decision for a radical resection (i.e., pancreaticoduodenectomy) or a local resection was made primarily by the attending surgeon based on a variety of factors, including tumor size, location (D1/2/3/4), and especially the proximity to the mesenteric border.

TNM stage, as defined by American Joint Committee on Cancer [AJCC] 6th, 7th, 8th edition, was used for tumor staging ⁹⁻¹¹. Contrast-enhanced thorax, upper and lower abdominal computed tomography were performed for staging and PET-CT was added to screening tests in suspicious cases.

In tumor markers, the upper limit of the normal range for CA19-9 was 0-27 U/Ml in our hospital and 0-6,5 ng/mL For CEA.

We considered unplanned re-operation as a surgical procedure under general, spinal or epidural anesthesia within 30 days of index operative procedure for any reason except follow-up procedures based on pathology results, in accordance with the ACS NSQIP definition ¹².

Wound infection was defined as superficial or deep incisional surgical site infection according to the definition of the Centers for Disease Control (CDC)¹³.

Perioperative mortality was defined as death within 30 days postoperatively or during hospital stay.

Anastomosis leakage was defined as a deterioration in the integrity of the anastomosis documented by the combination of clinical, radiological and operative tools.

All patients were treated with low molecular weight heparin, prophylactic antibiotherapy and compression stockings during induction of anesthesia as antithrombotic therapy. Postoperative follow-up was performed in the intensive care unit until hemodynamic stability was achieved. Discharge criteria included meal tolerance without nausea or vomiting, defecation, adequate pain control with oral analgesia, and independent mobilization. This work has been carried out in accordance with the Declaration of Holgiphi (2000) of the World Medical

Declaration of Helsinki (2000) of the World Medical Association. Before the operation, patients were informed about the operation and written consent was obtained.

STATISTICAL ANALYSIS

Data were analyzed using IBM SPSS Statistics for Windows, version 24 (IBM Corp., Armonk, N.Y., USA). Categorical measurements were summarized as numbers and percentages, and continuous measurements were summarized as mean and standard deviation (median and minimum-maximum where necessary). Kaplan-Meier analysis and Log Rank test were used for survival analysis.

Results

Nine patients with a mean age of 54.7 participated in the study. 55% of the patients were male. The most common ASA score was 3 (n. 5, 56%). Mean BMI was 23.7. The most common presenting symptom was abdominal pain (n. 6, 67%). Mean tumor marker levels measured preoperatively were 8.1 for CEA and 46 for CA19-9. Demographic and clinical characteristics are shown in Table I.

TABLE I - Demographic and Clinical Characteristics

Variable		N (%)
Age ± sd (min-max)		54.7+6.8 (49-63)
Sex	Male	5 (55)
	Female	4 (45)
ASA score	1	1 (11)
	2	3 (33)
	3	5 (56)
BMI ± sd (min-max)		23.7+2.7(20-29)
Presenting symptom	Abdominal pain	6 (67)
	Vomiting	2 (22)
	Weight loss	1 (11)
Preoperative CEA ± sd (min-max)		8.1+12.3 (1.01-40.1)
Preoperative Ca 19.9 ± sd (min-max)		46+29.8 (7.79-100.1)

The most common tumor localization was d2-3 (n. 7, 78%), and the most common surgical operation was pancreaticoduodenectomy (n. 7, 78%). the mean operative time was 340 min. the mean amount of intraoperative bleeding was 250 ml. there were no intraoperative complications. additional organ resection was performed in three patients. the details regarding the operations are shown in Table II. The mean tumor diameter was 3.5 cm. The mean num-

ber of lymph nodes dissected was 8.3 and the mean number of metastatic lymph nodes was 2. Most common T stage is T4 with 67%. The most common N stage is N0 with 56%. The most common pathological evaluation was moderately differentiated (n. 4, 45%). The pathological stages and tumor characteristics of the patients are shown in Table III.

TABLE II - Operation Details

Variable	C	N (%)
Tumor localization	D1 D2-3 D4	1 (11) 7 (78) 1 (11)
Operation type	Pancreaticoduodenectomy Pancreas protecting duodenectomy Segmental duodenum resection	7 (78) 1 (11) 1 (11)
Operation duration (min) Intraoperative bleeding (ml) Intraoperative complications		340+68 (220-420) 250+100 (100-450) 0
Additional organ resection	Right colon Liver Partial small intestine and colon	1 (11) 1 (11) 1 (11)

TABLE III - Pathological characteristics

Variable		N (%)
Tumor diameter (cm)		3.5+1.88 (2-8)
Total number of removed lymph nodes (mean) (min-max)		8.3+7.6 (0-22)
Number of positive lymph nodes (mean) (min-max)		2+3.4 (0-10)
T stage	T1	0
	T2	1 (11)
	T3	2 (22)
	T4	6 (67)
N stage	N0	5 (56)
	N1	2 (22)
	N2	2 (22)
Stage	Ι	1 (11)
0	IIA	2 (22)
	IIB	2 (22)
	IIIA	2 (22)
	IIIB	1 (11)
	IV	1 (11)
Pathological grade	Poorly differentiated	2 (22)
	Moderately differentiated	4 (45)
	Well differentiated	3 (33)

Table IV -	Postoperative	characteristics
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Variable		N (%)
Postoperative complication	Pancreatic fistula	3 (33)
	Anastomosis leakage	1 (11)
	Wound site infection	2 (22)
Postoperative hospitalization duration (day)		21.8+8.6(9-38)
Reoperation	Anastomosis leakage	1 (11)
30-day mortality	-	1 (11)
90-day unplanned hospital admission	Wound site infection	2 (22)
	Abdominal pain	1 (11)
	Diarrhea	1 (11)
Local recurrence		1 (11)
Systemic metastasis	Liver	1 (11)
	Bone	1 (11)
Current clinical status	Alive	4 (45)
	Death due to cancer	3 (33)
	Death due to causes other than cancer	2 (22)
Mean survival (month)		40+37 (1-117)



Fig. 1: Overall Survival.

The most common postoperative complication was pancreatic fistula (n. 3, 33%). The mean length of stay was 21.8 days. One patient was re-operated due to anastomotic leakage. One patient developed septic shock and died in the 30-day mortality period. The most common cause of unplanned admission to the hospital within ninety days was wound infection (n. 2, 22%). One patient developed local recurrence and two patients had systemic metastasis. In the current clinical situation, 4 (45%) patients are alive, 3 (33%) had cancer-related deaths, and 2 (22%) had non-cancer-related deaths. We found an average survival of 40 months.

Postoperative characteristics are shown in Table IV. Survival curves are shown in Fig. 1.

Discussion

Primary neoplasms of the small intestine, which make up 90% of the mucosal surface area of the gastrointestinal tract, are extremely rare. The duodenum, which constitutes only 4% of the small intestine, has a relatively high proportion of all tumors compared with jejunum and ileum. Primary malignant duodenal tumors account for only 0.3% of all gastrointestinal tumors, while they account for about 50% of all small bowel malignancies. ¹⁴

PDAC is rare and is generally considered to have low resectability and poor prognosis ¹⁵⁻¹⁷. PDAC appears quietly and has no specific symptoms at an early stage. When advanced, it may show symptoms of peptic ulcer (epigastric pain and discomfort), gastrointestinal bleeding (melena, hematochezia and hematemesis and anemia), gastrointestinal obstruction (vomiting, postprandial abdominal discomfort)¹⁷. In the series of Malleo G. et al, the main clinical symptoms were abdominal pain and epigastric pain (70.3%), weight loss (62%), and nausea/vomiting (35.1%) (4). The most common symptom in our series was abdominal pain (67%). In the series in the literature, male sex was predominant in primary duodenal tumors and the mean age ranged from 63 to 67 years ^{19,20}. While the patients in our series had a smaller mean age than the literature, male sex was dominant as in the literature.

The debate about the optimal surgical approach to duodenal cancers continued for years. Some authorities have claimed that only the Whipple procedure provides cancer-free surgical margins and appropriate regional lymph node resection. Alternatively, in some cases, segmental resection may be a suitable alternative, especially for distal or proximal duodenal adenocarcinoma ¹⁹. Palliative surgical interventions include: biliary, gastric and jejunal bypass and jejunalstomy ³⁵. These treatments should be reserved for patients with advanced disease or patients with poor clinical condition or geriatric patients with high operative risk. In any case these interventions are preferable to non-surgical palliative procedures, as they improve survival ²¹.

Curative resection in PDAC management remains the only option for treatment, but is not always feasible in patients with locally advanced tumors or when tumors invade the mesenteric root. Pancreatoduodenectomy is the most appropriate operation to achieve complete resection when a tumor is found in the second part of the duodenum. Some authors suggest that all duodenal cancers should be treated with pancreaticoduodenectomy because regional lymph nodes are completely eliminated by this procedure ^{22,23}. Although it is difficult to perform a well-defined regional lymphadenectomy in the region due to lack of duodenal mesentery, removal of all periduodenal soft tissues removes a sufficient number of lymph nodes in most patients. For tumors located in the first, third or fourth sections of the duodenum, complete resection can be achieved by removing the affected segment ²⁴.

Some authors reported excellent survival following segmental resection and significantly reduced postoperative mortality and morbidity. Bakaeen et al. compared 50 patients treated with radical resection and 15 patients treated with limited resection, and found similar postoperative morbidity and generally similar results. In the limited resection group in their study, the length of hospital stay was significantly shorter ²⁵. Similarly, Tocchi et al. found that patients treated with segmental resection had postoperative morbidity and mortality, shorter hospital stay, and an equivalent overall survival ²⁶. On the other hand, there are studies that claim that segmental resection results in insufficient resection margins and incomplete regional lymphadenectomy. Sohn et al. compared 35 patients who underwent PD with 13 patients undergoing pancreatic protective duodenectomy and found long-term survival significantly improved in the PD group (5-year rates, 63% to 0%). Additionally, in this study, the segmental resection group had significantly higher positive surgical margin rates (23% vs 3%)²².

In our series, as recommended in the literature, we performed PD for tumors located in the Duodenum 2-3 region. We performed pancreatic protective duodenectomy for D1 localized tumors and segmental resection for tumors localized at the distal duodenum. We performed additional organ resections due to tumor invasion.

The importance of adequate lymphadenectomy has long been recognized. J. M. Cloyd et al. found that an increasing number of LNs removed during surgery are associated with a gradual increased survival ⁷. However, the optimal LN number was not well established. Although AJCC guidelines recommend the evaluation of at least six LNs for duodenal or small intestinal adenocarcinoma, some authors have questioned whether to increase

the minimum number of LNs to be examined ^{10,27}. In our study, the mean number of dissected lymph nodes was 8, whereas the mean number of pathological lymph nodes was 2. In the series of T. Sakamoto et al., 56% of the patients had T3/T4 tumor and 47% were lymph node positive. They found T stage, N status of tumor to be associated with long-term survival (28). Poultsides GA et al. found a five-year survival rate of 68% in Nodenegative (N0) patients and 17% in patients with N2 disease ²⁹. While the lymph node positivity in our series was similar to the literature, the T stage of our patients was considerably higher than the literature, and only 11% of our patients had T1/T2 tumors. The pathological grade of the patients in our series was most commonly moderately differentiated (45%) similar to the series in the literature 6,28,29. In the series in the literature, tumor diameter ranged from 2.5 to 4.25 cm, although giant tumors such as 20 cm were also encountered 4,15,30,31. Kawahira, H et al. found that patients with a tumor diameter greater than 5 cm underwent more frequent palliative surgery and had a lower 5-year survival rate (72% vs 5%) 32 . The mean diameter of the tumors in our series was 3.5 cm. Our largest tumor was 8 cm in diameter and this patient required additional organ resection.

In the studies in the literature, postoperative complication rate was 12-53%, pancreatic fistula rate was 3-16% and postoperative hospital stay ranged between 14-18 days ^{4,15,29}. These studies are heterogeneous in terms of performed surgery and in previous series in the literature, postoperative morbidity and length of hospitalization have been shown to change with the type of surgery applied ^{25,26}. In our series, the rate of segmental resection was lower than the studies in the literature and therefore our morbidity and pancreatic fistula rate was high. In our series, postoperative morbidity rate was 66% and the most common cause of morbidity was pancreatic fistula, seen in 33% of the patients. Although the postoperative hospitalization duration was 21 days and was higher than the literature, the patients who underwent conservative follow-up for pancreatic fistula were responsible for these prolonged hospitalizations. We reoperated the patient who developed anastomosis leakage. This patient died in the postoperative period due to septic shock. Reasons for unplanned re-admission to the hospital was led by wound site infection.

The literature shows that the 5-year survival rates for pancreatic cancer, bile duct cancer, ampullary cancer, and duodenal cancer are 14–15%, 27%, 39–42% and 59%, respectively ^{33,34}. Although periampullary cancers have a similar cancer spread pattern, duodenal adenocarcinomas are thought to have positive results compared to pancreatic, distal bile duct and ampulla Vater cancer. In the S. Y. Lee et al series, the median survival of 41 patients who underwent curative resection was 25.1 months (4-134 months). Of these, 21 were still alive, with an average survival of 35.8 months (16-124 months) ³⁵.

Although the mean survival was 40 (1-117) months in our series, 45% of our patients were still alive. Three patients died due to cancer-related causes and two patients died due to septic shock and cardiac problems. During our follow-up, one patient developed local recurrence, one patient had liver metastasis and one had bone metastasis. We think that duodenal adenocarcinomas exhibit relatively better biological behavior than other periampullary cancers.

The most important limitation of our study was that it was retrospective, as other studies in the literature, and had limited number of patients. Our results from a single academic medical center do not reflect the practice of most institutions. However, our study provides a perspective in the treatment of this rare disease.

Conclusions

In conclusion, surgical resection can be performed safely in PDAC patients and offers a favorable long-term outcome. Pancreatoduodenectomy continues to be the preferred procedure for tumors located in the second part of the duodenum and locally advanced tumors in other duodenal regions. Segmental resection may be appropriate for selected patients, especially for distal duodenal tumors.

Riassunto

Questo studio è finalizzato a presentare la nostra esperienza su pazienti sottoposti a trattamento chirurgico curativo per l'adenocarcinoma duodenale primario.

Lo studio è stato effettuato sui pazienti con diagnosi di adenocarcinoma duodenale primario trattati tra il 2006 e il 2018. Sono stati valutati retrospettivamente le caratteristiche demografiche e cliniche dei pazienti, i dettagli dell'operazione, le caratteristiche patologiche dei tumori, i risultati di follow-up a breve e lungo termine e la sopravvivenza media.

Sono stati inclusi nello studio nove pazienti con un'età media di 54.7 anni: 55% dei pazienti era di sesso maschile. Il sintomo più comune al ricovero era il dolore addominale (n. 6; 67%). La localizzazione del tumore più comune è stata la D2-3 (n. 7; 78%) e l'operazione chirurgica più frequentemente eseguita è stata la pancreaticoduodenectomia (n. 7; 78%). Non ci sono state complicanze intraoperatorie in nessun paziente. Il diametro medio del tumore era di 3,5 cm. Il numero medio di linfonodi dissezionati era 8,3 e il numero medio di linfonodi metastatici era 2. La complicazione postoperatoria più comune era la fistola pancreatica (n. 3; 33%). La durata media della degenza è stata di 21,8 giorni. Un paziente è andato incontro a shock settico e mortalità seguita entro 30 giorni. La causa più comune di ricovero non programmato in ospedale entro 90 giorni

è stata l'infezione della ferita (n. 2; 22%). Un paziente ha presentato recidiva locale e due pazienti hanno presentato metastasi sistemiche. Abbiamo registrato una sopravvivenza media di 40 mesi.

La pancreaticoduodenectomia è l'approccio più comune quale chirurgia curativa con lunga sopravvivenza nonostante l'alto tasso di complicanze postoperatorie. Raccomandiamo dunque la resezione radicale nel trattamento chirurgico dell'adenocarcinoma duodenale primario.

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