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PANKREAS KANSERLERİNDE LAPAROSKOPİK VE AÇIK WHIPPLE PROSEDÜRÜNÜN KARŞILAŞTIRILMASI: TEK MERKEZ SONUÇLARI

LAPAROSCOPIC VERSUS OPEN WHIPPLE PROCEDURE FOR PANCREATIC ADENOCARCINOMA: A SINGLE-CENTER EXPERIENCE

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ABSTRACT

PURPOSE: The laparoscopic approach for pancreas tumors is not comprehensively approved, due to its technical complexity. The aim of this study was to compare the perioperative and postoperative results, oncological outcomes and survival of patients with a proximal pancreatic tumor who underwent laparoscopic treatment (TLPD) versus an open procedure (TPD).

MATERIAL AND METHODS: A retrospective evaluation was made of the data of patients who underwent pancreatic resection between 2009 and 2017. All patients undergoing total pancreaticoduodenectomy (TPD) or TLPD were included in this study. The patients were followed up for a minimum of 6 months postoperatively and all complicationswere recorded,and analysed according to the Clavien system categories.

RESULTS: TPD was applied to62 (80.5%) patients, and TLPD to 15 (19.4%). No significant differences were determined between the groups in respect of patient demographic data. Significant differences were determined in the TLPD group in respect of blood transfusion, blood loss, length of stay in hospital and intensive care unit (ICU), and thenumber of lymph nodes resected. Operating time was significantly longer in the TLPD group. Post-pancreatectomy hemorrhage was lower in the TLPD group, and there were no differences in respect of other complications.

CONCLUSION: The laparoscopic Whipple procedure is not only feasible but safe, with low morbidity and acceptable complication rates. TLPD is characterized by less blood loss, lower transfusion rates, improved lymph node resection, and less wound infection. However, the laparoscopic Whipple procedure should be applied in selected cases.

Keywords: *Laparoscopic pancreatectomy, open pancreatectomy, whipple*

ÖZET

AMAÇ: Pankreas tümörleri için uygulanan laparaskopik prosedür teknik olarak zor olduğu için yaygın olarak uygulanmamaktadır. Çalışmanın amacı, laparaskopik ve açık yöntemlerle proksimal pankreas tümörleri için ameliyat edilmiş hastaları, ameliyat öncesi bulguları, ameliyat sonrası bulguları, onkolojik sonuçları ve sağ kalım sürelerine göre karşılaştırmaktır.

GEREÇ VE YÖNTEM: 2009 ve 2017 tarihleri arasında pankreatik rezeksiyon yapılmış olan hastaların bilgileri toplandı. Açık (TPD) ve laparaskopik total pankreatikoduodenektomi (TLPD) yapılmış hastalar bu çalışmaya dahil edildi. Hastalar, ameliyattan sonra en az 6 ay takip edildi ve tüm komplikasyonlar değerlendirildi. Komplikasyonların tümü kaydedildi ve Clavien sistemine göre sınıflandırıldı.

BULGULAR: 62 (%80.5) hastaya TPD, 15 (%19.4) hastaya TLPD uygulandı. hastaların demografik bulgularına göre farklılıkları yoktu. TLPD grubunda, kan transfüzyonu, kan kaybı, hastanede kalış süreleri, yoğun bakımda kalma süreleri, çıkarılan lenf nodu sayıları açısından belirgin farklılıklar tespit edildi. Ameliyat süresi TLPD grubunda belirgin düzeyde uzundu. Pankreatektomi sonrası kanama TLPD grubunda düşüktü. Diğer komplikasyonlar açısından fark yoktu.

SONUÇ: Laparaskopik whipple prosedürü düşük morbidite ve kabul edilebilir düzeydeki komplikasyon oranı ile sadece uygulanabilir değil aynı zamanda güvenli bir yöntemdir. TLPD, düşük kan kaybı, düşük transfüzyon oranı, yüksek sayıda lenf nodu çıkarılması, düşük yara yeri enfeksiyonu riski ile karakterizedir. Buna rağmen TLPD, ancak seçilmiş olgularda uygulanabilmektedir.

Anahtar kelimeler: *Laparaskopik pankreatektomi, açık pankreatektomi, whipple*

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This study was approved by Local Ethics Committee of Selçuk University, Faculty of Medicine (approval date and number: 20.03.2019/ 2019-2)

PURPOSE

The laparoscopic approach has become the gold standard method for the treatment of achalasia, gallstones and gastroesophageal reflux disease. Laparoscopic operations are also performed in tumor surgery. In recent years, significant developments in minimally invasive surgery and laparoscopic technology have encouraged the use of laparoscopy in the treatment of other organs. However, the laparoscopic approach for head of pancreas tumors is not comprehensively approved, due to its technical complexity (1). Total laparoscopic pancreaticoduodenectomy (TLPD) can be performed on very few patients. Many surgeons use laparoscopy during resection, and then make the reconstructions with mini-laparotomy (1,2).An increasing number of recent studies have demonstrated that proximal pancreatic cancers may be treated with laparoscopic procedures (3).Many comparative studies have also reported the safety and feasibility of laparoscopic pancreaticoduodenectomy (4,5).

The aim of this study was to compare the perioperative and postoperative results, oncological outcomes and survival of patients with proximal pancreatic tumor who underwent laparoscopic treatment versus an open procedure.

MATERIAL AND METHODS

This study was approved by Local Ethics Commitee of Selçuk University, Faculty of Medicine (approval date and number: 20.03.2019 / 2019-2). A retrospective evaluation was made of the data of patients who underwent pancreatic resection between 2009 and 2017. The patient demographic data, operative variables, comorbidities, pathological findings, postoperative survival, operating times, estimated blood loss, and complications were retrospectively analyzed. All patients undergoing total pancreaticoduodenectomy (TPD) or TLPD were included in this study. All patients had pancreatic head carcinoma and no vascular invasionobserved on preoperative imaging.

The patients were followed up for a minimum of 6 months after surgery and all complications were analyzed. The complications wererecorded and categorised according to the Clavien system (6).Pancreatic fistula, delayed gastric emptying and hemorrhage were classified according to standard international consensus definitions (7).There were no objective criteria for the patients applied with TLPD. The selection of TPD or TLPD was based on patient choice after being fully informed about the surgical procedures.

TLPD was performed with the patient in the supine, split-leg position. A 12-mm trocar was entered at the supraumblicus level and pneumoperitoneum was applied. In the abdominal exploration, another three trocars (1x12-mm, 2x5-mm) were placed. First, the gastrocolic ligament was opened and the transverse colon was mobilized. The distal stomach and duodenum were lifted and resected with an endoscopic stapler (standard resection). The hepatic artery and portal vein were identified, then common bile duct was surrounded and transected. The superior mesenteric vein (SMV) and portal vein were determined at the inferior of the pancreas, over which a retropancreatic tunnel was constructed. The proximal area of thepancreas was transected. The Kocher manoeuvre was applied and the distal bowel was resected with an endoscopic stapler. The specimen was then removed en bloc through the enlargedtrochar incision, and sent to the pathology laboratory for frozen-section examination. Hepaticojejunostomy was performed followed by pancreaticojejunostomy, and finally, gastrojejunostomy. All anastomoses were applied as single layer with non-absorbable sutures. A single drain was placed behind the reconstructed area.

Statistical Analysis

The data collected were recorded on Microsoft Excel 2007 (Microsoft, Redmond, WA, USA) and analysed using the Statistical Package for the Social Sciences version 20.0 software(SPSS, Inc., Chicago, IL, USA). For continuous variables, descriptive statistics were calculated and expressed as mean±standard deviation. Categorical variables were presented as number and percentage. Comparsions between the TPD and TLPD patients were made using Fisher's Exact test or the Chi-square test. Continuous variables were evaluated with the Mann Whitney-U test or student's t-test at a level of 0.001 statistical significance

RESULTS

Of the initial 82 patients, 5 were excluded; 1 due to mucinous cystadenoma, 1 due to leiomiyoma, and 3 because of obstruction necessitating conversion to an open surgical procedure. TPD was applied to 62 (80.5%) patients and TLPD to 15 (19.4%). The demographic data of the patients are shown in **Table 1.** Age, gender, body mass index and medical comorbidities were similar in both groups. Operative variables and tumor location and size are given in **Table 2.** Operating times were significantly longer in the TLPD group than in the TPD (median 312±24 vs 263±12 min, $p<0.001$). Median estimated blood loss(median 163 vs 460 mL, $p<0.001$), and amount of blood transfusion(20 vs 45 %, $p=0.003$) were lower, and thelength of stay in ICU (median 1.28±1.4 vs 2.3±2 days, $p=0.012$), and overall length of stay in hospital(median 9.6 vs 13.3 days, $p<0.001$)were considerably shorter in the TLPD group than in the TPD group.

Postoperative outcomes for both groups are shown in **Table 3.** The morbidity rate was similar in the TPD and TLPD groups. Mortality was seen in 3 (4.8%) patients in the TPD group and in none of the TLPD group. There were no cases of intraoperative mortality. According to the Clavien Grade classifications, minor complications(grade 1,2)were seen at the rate of 66.6% in the TLPD group and 65.5% in the TPD group. Major

complications(grade 3-5)were seen at similar rates in both groups. Pancreatic fistula (grade B,C), and post-pancreatectomy hemorrhage(grade B) were seen in the TPD group. The rates of delayed gastric emptying were similar in both groups. Re-operation was necessary in1 patient in the TLPD group because of intra-abdominal abscess, and laparoscopic drainage was applied. In the TPD group, 2 patients underwent reoperation because of abscess and 2 patients who were found to have internal herniation with small bowel obstruction were reoperated on for hernia reduction. A total of 9 (14.5%) patients in the TPD group had intra-abdominal abscessbut not all were reoperated. The patients with no sepsis signs were not reoperated on. Wound infection was determined at a significantly higher rate in the TPD group(p=0.005).

The oncological outcomes are presented in **Table 4.** No significant difference was determined between the groups in respect of tumour size, N stage, and R0 resection. In the TLPD group, the number of resected lymph nodes was higher than in the TPD group(p<0.001). There was no difference between the groups in respect of the mean time from surgery to starting chemotherapy (60±2.4 vs 62±1.8 days). Recurrence was determined in26.6% of the TLPD group and in 29% of the TPD group.

Table 1: Demographics and comorbidity of patients who underwent open pancreaticoduodenectomy (TPD) and laparoscopic pancreaticoduodenectomy (TLPD)

Variable	TLPD n: 15 (%19.4)	TPD n: 62 (80.5%)	p value
Age*	65.5 ±11.3	67.7 ±13.4	0.954
BMI*	25.7 ± 5.13	24.5 ± 4.01	0.358
Gender#			
female	9 (60)	45 (72.5)	0.512
male	6 (40)	17 (27.5)	0.622
Hypertansion#	10 (66)	38 (61.2)	0.124
Diabetes mellitus#	9 (60)	21 (33.8)	0.754
cardiac disease#	4 (26.6)	12 (19.3)	0.156
ASA#			
1 and 2	4 (26.6)	18 (29)	0.842
3	10 (66.6)	42 (67.7)	0.958
4	1 (6.6)	2 (3.2)	0.245

ASA, American Society of Anesthesiologist; BMI, body mas index; Datas are expressed as * mean ± standard deviation, # n (%), [a] p < 0.001

Table 2: Operative variables and tumor's features of patients who underwent open pancreaticoduodenectomy (TPD) and laparoscopic pancreaticoduodenectomy (TLPD)

Variable	TLPD n: 15 (%19.4)	TPD n: 62 (80.5%)	p value
tumor location#			0.224
head	15 (100)	60 (96.7)	
ampulla	0	2 (3.2)	
duodenum	0	0	
preoperative chemotherapy#			0.546
yes	1 (6.6)	5 (8)	
no	14 (93.3)	57 (91.9)	
tumor size*	2.4±1.5	2.6±1.5	0.916
blood transfusion#	3 (20)	28 (45)	0.003
estimated blood loss (mL)*	163±35	460±5.2	<0.001[a]
operative time (min)*	312±24	263±12	<0.001[a]
ICU stay median, day*	1.28±1.4	2.3±2	0.012
lenght of hospitalization day*	9.6±1.2	13.3±4.2	<0.001[a]

ICU: Intensive care unit. Datas are expressed as * mean ± standard deviation, # n (%), [a] p < 0.001

Table 3: Postoperative complications of patients who underwent open pancreaticoduodenectomy (TPD) and laparoscopic pancreaticoduodenectomy (TLPD)

Variable	TLPD n: 15 (%19.4)	TPD n: 62 (80.5%)	p value
Complication#			0.856
yes	13 (86.6)	54 (87)	
no	2 (13.3)	8 (12.9)	
complication Clavien grade#			0.073
none	2 (13.3)	8 (12.9)	
1	4 (26.6)	16 (25.8)	
2	6 (40)	24 (38.7)	
3	2 (13.3)	9 (14.5)	
4	1 (6.6)	2 (3.2)	
5		3 (4.8)	
pancreatic fistula#	1 (6.6)	5 (8)	0.646
grade A	1 (6.6)	3 (4.8)	
grade B	0	1 (1.6)	
grade C	0	1 (1.6)	
postpancreatectomy hemorragy#	0	2 (3.2)	<0.001[a]
grade A	0	0	
grade B	0	2 (3.2)	
grade C	0	0	
delayed gastric emptying#	3 (20)	14 (22.5)	0.741
grade A	2 (13.3)	12 (19.3)	
grade B	1 (6.6)	1 (1.6)	
grade C	0	1 (1.6)	
Reoperation#	1 (6.6)	4 (6.4)	0.963
wound infection#	2 (13.3)	24 (38.7)	0.005
intra-abdominal abscess#	1 (6.6)	9 (14.5)	0.082

Datas are expressed as * mean ± standard deviation, # n (%), [a] p < 0.001

Table 4: Pathologic findings of patients who underwent open pancreaticoduodenectomy (TPD) and laparoscopic pancreaticoduodenectomy (TLPD)

Variable	TLPD n: 15 (%19.4)	TPD n: 62 (80.5%)	p value
tumor stage#			0.365
T1	7 (46.6)	25(40.3)	
T2	5 (33.3)	23(37.0)	
T3	3 (20)	14 (22.5)	
T4	0	0	
N stage#			0.546
N0	4 (26.6)	22 (35.4)	
N1	11 (73.3)	40 (64.5)	
surgical magrin#			0.518
R0	14 (93.3)	57 (91.9)	
R1-2	1 (6.6)	5 (8)	
number of lymph nodes resected*	19 ±11	11.5±12	<0.001
recurrence#			0.423
yes	4 (26.6)	18 (29.0)	
no	11 (73.3)	44 (70.9)	

Datas are expressed as * mean ± standard deviation, # n (%), [a] p < 0.001

DISCUSSION

Laparoscopic applications have decreased surgical morbidity in several operations, although laparoscopic pancreaticoduodenectomy is a new surgical procedure which has not yet achieved a safe consensus regarding the surgical benefits (8,9).The first case was described in 1994 but laparoscopic pancreaticoduodenectomy has been slow to gain popularity (10).TLPD is a challenging procedure because of the difficulties inreaching and exposingthe pancreas, which is localised in the retroperitoneum, hemorrhage control, and reconstruction of pancreatic and biliary remnants. A minimally invasive procedure is usually preferred to open surgery as recovery time is shorter and wound complications are fewer (11).

The current study groups were similar in respect of gender, comorbidities, body mass index, and ASA scores. Previous studies have compared the outcomes of patients who have undergone TPD or TLPD (11,12,13).According to those studies, the TLPD grouphad a significantly shorter length of stay inhospital, a shorter stay in ICU, less blood loss and need for blood transfusion, and a higher number of lymph nodes removed. However, operating times were significantly longer for TLPD groups, but there was no difference in respect of complications between TLPD and TPD. The current study results are consistent with these findings in literature.

TLPD is associated with a long operating time because there is a substantial learning curve. Surgeons performing TLPD have proposed a staged learning process, with a decrease in performance measures that progress in difficulty as the surgeon's skill improves. For example, mean operating time was reported to be reduced from from 9.8 hrs to 6.6 hrs, by Kim et al (14) and from 7.7 hrs to 5.3 hrs by Kendrick et al.(15). In the current study, the mean operating time was 312 mins(range, 300-360 mins) for TLPD, and 263 mins(range, 210-330 mins) for TPD. These operating times were longer in the first operations than in the later ones, and the mean value was shorter than previous reports in literature.

Blood loss and transfusion may have some sequelae, because blood transfusion may leave the host immune system defenceless against recurrence and metastasis of primary tumors(16).A retrospective study showed that5-year survival was decreased in patients who received 3 or more units of transfused blood (16).A similar negative biological effect of blood transfusion on cancer recurrence has been reported for other gastrointestinal malignancies(17,18).In previous studies, minimally invasive pancreatoduodenectomy has also resulted in decreasedbloodlossandtransfusionrequirements(12,19). Decreased intraoperative blood loss and requirement for blood transfusion have also been attributed to the better visualization with a laparoscope(4).Visualization of major and minor vascular tissues facilitates the operation. It has been previously reported that TLPD groups had less intraoperative blood loss (1.032 vs. 195 cc)(1.452 vs. 841.8 cc)and a lower transfusion requirement(4.7 vs. 0.64 U).(5)In the current study, mean intraoperative blood loss was significantly less in the TLPD group than in the TPD group (163 cc vs.460 cc).

In the current study, length of stay in hospital and ICU were significantly shorter in the TLPD group (1.28-2.3 days and 9.6-13.3 days). Croome et al.(20) also emphasised the advantages of TLPD, and several studies have shown that duration of hospital stay is shorter in TLPD groups(4,21,22).This shorter stay can be attributed to a decreased wound infection rate, blood loss and transfusion rate, and early recovery after TLPD. Recent meta-analyses and reviews have confirmed these findings (21,22).

With the exception of wound infection and the development of intra-abdominal abscess, there was no significant difference between the current study groups in respect of overall morbidity and mortality rates. Song et al.(23)showed that major complications, including pancreatic fistula and delayed gastric emptying were similar in two groups. The mostfrequent morbidities of pancreatic transectionhave been reported to be delayed gastic emptying (19%-23%), anastomotic fistula from the pancreas (9%-18%), abdominal abscess(9%-10%), and intra-abdominal or gastrointestinal hemorrhage(24,25). Pancreatic fistula has been determined at the rate of 18% for TLPD and at 2-30% for TPD(26).Risk factors for pancreatic fistula are soft pancreatic parenchyma(27,28) and pancreatic duct<3mm in diameter (27,28).In the current study, duct size was not seen to have an impact on the leakage rate, because all the patients hadsoft pancreatic tissue with 3mm or smaller ducts. There was only 1 grade A pancreatic fistula in the TLPD group. A previous studyshowed that the risk of pancreatic fistula was low in patients with fibrotic pancreas and dilated duct who were applied duct-to-mucosa anastomosis, whereas end-to-end invagination was safer in patients with non-fibrotic pancreas tissue and a small duct(29). In another series, the incidence of pancreatic fistula rate was 6.25% in the patients who were applied duct-to-mucosa anastomosis, and 19.6% in the invagination group(30).In the current study, end-to-end invagination was applied to both groups. The pancreatic fistula rate was 6.6% in the TLPD group and 8% in the TPD group, which was lower compared to literature. Ultrasound-guided percutaneous drainage was applied to grade A and B pancreatic fistulas, and surgical peripancreatic drainage was applied to a grade C pancreatic fistula patient in the TPD group.

Several studies have shown a higher incidence of delayed gastric empty (DGE) after pylorus preserving operations compared to classic methods(31,32).Operative methods may also impact the rate of DGE, and with the method of reconstruction (antecolic and retrocolic) after pylorus preserving methods for devascularization and denervation of the pylorus, DGE may be associated with pancreatic fistula and peripancreatic collection(33,34,35).

In the current study, there were 14 (22.5%) patients in the TPD group and 3 (20%) patients in the TLPD group with DGE. Intra-abdominal abscess was determined in 14 of these 17 patients (82.3%). This rate of DGE was similar to findings in literature(24,25).This morbidity was resolved with percutaneous drainage of the intra-abdominal abscess. However, Grade C DGE were not treated, and Grade B DGE patients were treated with medical follow-up over a mean period of 6 months.

Tien et al differentiated postpancreatic hemorrhage(PPH) as early (<1 week), and late(>1 week). Postpancreatic hemorrhage may arise from venous or arterial vessels, suture lines of the anastomoses, areas of resection, eroded pseudoaneurysms or hemobilia from endobiliary stents(36).Cullen et al reported hemorrhage in 12% of the patients with anastomotic leakage, whereas no hemorrhage developed in patients without anastomotic leakage(37).Studieshave also shown a positive correlation between leakage and hemorrhage(24).In the current study, 2 patients had grade B PPH and these patients had grade B or C pancreatic fistula. A second likely mechanism may be intra-abdominal infection and abscess in the abdomen(38).There were no patients in the current study with this mechanism.

A larger study comparing TPD to TLPD demonstrated increased lymph node harvest (16 vs 23 lymph nodes) (4).In contrast to other studies, there was no difference between the groups in negative resection margin status or the number of positive lymph nodes harvested(4). In the current study, improved lymph node harvest was determined with TLPD compared with TPD (19 vs 11.5 lymph nodes). The technical imaging of TLPD is more appropriate for better visualization, as the lymph node groups posterior to the portal vein and behind the artery, between the SMA and SMV, may be better visualized with TLPD(39).

CONCLUSION

The principle disadvantage of the TLPD procedure is the difficult and lengthy learning cuve required. Nevertheless, the laparoscopicWhipple procedure is not only feasible but safe, with low morbidity and acceptable complication rates. TLPD is characterized by less blood loss, lower transfusion rates, improved lymph node resection, and less wound infection. However, the laparoscopic Whipple procedure may be applied in selected cases.

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