Anastomotic leaks at the pancreaticojejunostomy following pancreaticoduodenectomy in patients with pancreatic head adenocarcinoma increases the local recurrence rate

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INTRODUCTION: In contrast to colorectal cancer patients, the effect of anastomosis leakage following pancreatic adenocarcinoma surgery on survival and recurrence rate is not clear. The present study aimed to determine the effect of pancreaticojejunostomy (PJ) anastomosis leakage, especially on the local recurrence rate and time of recurrence, in patients that underwent pancreaticoduodenectomy (PD) for pancreatic adenocarcinoma.

MATERIALS AND METHODS: This retrospective study included 64 pancreatic adenocarcinoma patients that underwent PD between January 2007 and August 2015. PJ anastomosis leakage was evaluated based on International Study Group on Pancreatic Fistula criteria. The effects of PJ anastomosis leakage on local recurrence, disease-free survival, and overall survival were assessed.

RESULTS: Among the patients, 44 were male and 20 were female, and median age was 61(39-84) years. In all, 11 patients developed PJ leakage. Local recurrence occurred in 5 (45.4%) of the patients that developed PJ leakage, versus in 4 (7.5%) of the patients without leakage (p=0.02). Local recurrence developed earlier in those with leakage than in those without (p= 0,013). In contrast, there weren't any significant differences in disease-free survival, or overall survival.

CONCLUSION: PJ leakage seems to be associated with more frequent and earlier local recurrence while it did not influence survival.

KEY WORDS: Leakage, Pancreatic cancer, Recurrence

Introduction

Pancreatic cancer is one of the most aggressive cancers. Although surgical resection is the only definitive treatment option for pancreatic cancer, it is known that pancreaticoduodenectomy (PD) is associated with morbidity and mortality rates as high as 40%-50% and 5%, respectively. Pancreaticojejunostomy (PJ) leakage is the most critical complication following PD, occurring in 12%-20% of patients. It may be associated with crucial conditions, such as abscess and vascular problems. In addition to the early postoperative complications, PJ leakage also increases the length of hospital stay and the cost. However, the effect of PJ leakage on long-term outcomes is not clear. Recurrence is one of the most important factors associated with worse long-term outcomes. Several studies on the long-term effects of anastomotic leak in patients who underwent surgery for esophageal and colorectal cancers reported that it has a negative prognostic effect on tumor recurrence due to suppression of cellular immunity. Likewise, it was suggested that the presence of anastomotic leak increases secre-
tion of pro-inflammatory cytokines weakening cellular immunity and enhancing the growth of cancer cells that remain at the microscopic level. However, a limited number of studies have reported contradictory effects of PJ leakage on recurrence. In the present study, we aimed to determine effect of PJ anastomosis leakage following PD on local recurrence, disease-free survival, and overall survival.

Materials and Methods

The study was approved by the Institutional Review Board of the Uludag University School of Medicine. Data for patients who underwent PD between January 2007 and August 2015 were retrospectively reviewed. Patients who were diagnosed with histopathologically proven pancreatic ductal adenocarcinoma (PDA) located at the pancreatic head were enrolled in the study. Patients who underwent PD for other indications, received neoadjuvant therapy and/or chemotherapy, tumor location other than pancreatic head, died while hospitalized, were unavailable to undergo R0 resection, or underwent vascular reconstruction due to portal vein invasion were excluded from the study. Patient demographics, histopathological data, short-term outcomes such as abscess due to PJ anastomosis leakage, and long-term outcomes such as survival and recurrence were investigated. Tumors were staged according to the TNM staging system. Intra-operative frozen-sections obtained from both pancreatic and choledochal surgical margins were examined. Negative surgical margins were verified based on both intra-operative examination of frozen-sections and postoperative histopathological examination. All of the patients underwent standard or pylorus-preserving PD surgery. PJ anastomosis was performed as end-to-side ductojejunostomy. Ductojejunostomy anastomosis was performed as a double-layer. Posterior and anterior aspects of the anastomosis site were sutured via continuous suturing with prolene sutures, whereas interrupted sutures using PDS suture material was performed in cases of duct-mucosa anastomosis. None of the patients had a stent placed. Active vacuum drains were placed in all patients. Pancreatic fistula (PF) was investigated as an early postoperative outcome. Amylase analysis of drainage fluid was performed in clinically suspicious patients for PJ leakage. The diagnosis of PF was based on the presence of an amylase concentration in drainage fluid 3-fold greater than that in serum. PF was graded as A, B, and C, according to International Study Group on Pancreatic Fistula criteria (ISGPF). Local recurrence was defined as presence of radiologically detectable mass in the pancreatic resection bed in abdominal CT scan or PET-CT. The local recurrence rate, distant metastasis, disease-free survival, and overall survival were evaluated as long-term outcomes.

Results

In total, 220 patients underwent PD during the study period. Ninety of them had histopathologically proven PDA. Eighteen patients without follow-up, 7 with in-hospital mortality, and one who underwent R1 resection were excluded. Of the 64 remaining patients that were included in the study, 52 underwent standard PD and 12 underwent pylorus-preserving PD. There were 20 females and the median age was 61 (39-84). PJ anastomosis leakage was diagnosed in 11 (17%) of the 64 patients. According to ISGPF classification, 4 patients had grade A and 7 had grade B PF. Daily volume of drainage fluid from intraabdominal drains ranged from 300 mL to 700 mL. All the patients with grade A and

![Fig. 1: Time to local recurrence in the patients with and without PJ leakage. PJ leakage was observed in 11 patients. Mean time to local recurrence was 32.8 months in the patients with leakage group (95% CI: 16.5-49.1), versus 54.3 months in those without leakage group (95% CI: 45.8-62.8) (P = 0.007).](image-url)
one patient with grade B PF were conservatively followed-up. Additional percutaneous drainage procedures (abcess drainage or percutaneous biliary drainage) were necessary in the remaining 6 patients with grade B PF.

Table I shows the demographics and characteristics, and TNM staging in the patients with and without PJ anastomosis leakage. Local recurrence occurred in 5 patients in the PJ(+) leakage group, and 4 in the PJ(–) leakage group (p=0.02). Local recurrence developed earlier in the patients with PJ leakage than in those without PJ leakage (Fig. 1), whereas there were not any significant differences in overall survival, or disease-free survival between the 2 groups (Table II).

Local recurrence was diagnosed earlier in patients with PF comparing to the patients without fistula (33.9± 8.2 vs. 44.7± 4.4 months, p= 0.01). Vascular invasion was another factor associated with early local recurrence (17.3± 8.8 vs. 45.1± 3.9, p=0.02). However, presence of PF was the only risk factor for local recurrence [HR: 9.5 (2.3- 39.4), p= 0.02].

Discussion

In the present study local recurrence occurred in 45.4% of the patients with PJ anastomosis leakage, versus in 7.5% of those without PJ anastomosis leakage. In addition, there wasn’t a significant difference in disease stage between the patients with and without anastomosis leakage, whereas local recurrence did differ significantly. Likewise, the local recurrence rate and early development of local recurrence rate were significantly higher in the patients with PJ anastomosis leakage. In the present study, PJ anastomosis leakage was associated with early local recurrence, whereas it did not influence survival. The 5-year survival rate following surgical resection in pancreatic cancer patients is only 10%-20%, even in large series 19,20. Local recurrence without distant metastasis occurs in 30% of patients. Factors strongly associated with local recurrence include positive surgical margins, capsule invasion, and lymph node metastasis 21. The impact of PJ leakage on local recurrence and survival in patients with pancreatic cancer has been the focus of recent research, but the number of such studies is limited in English literature. A retrospective study that reported that PJ leakage occurred in 9 of 47 patients, 8 of whom developed recurrence, and that mean survival was 16.5 months 16. The findings showed that anastomotic leak did not have a significant effect on local recurrence or survival. In another study comparing 152 pancreatic head resections and 32 distal pancreatic resections, Nagai et al. 18 reported that PF was an independent prognostic factor for peritoneal recurrence. Recently, Assifi et al. 17 reported that PF in patients that underwent PD for PDA did not significantly affect recurrence-free survival or overall survival.

Most published studies suggesting that anastomosis leakage increases local recurrence rates and decreases survival have been on colorectal cancers. Ptok et al. 22 studied 1741 rectal cancer patients and reported that the local recurrence rate was higher and 5-year survival was shorter in the patients with anastomosis leakage. Various hypotheses have been theorized to explain these correlations. One suggests that exfoliative tumor cells that accumulate in the bowel lumen are implanted into the pelvis during anastomotic leak 23,24. Another hypothesis suggests that the inflammatory process during anastomotic leak enhances angiogenesis and recurrence. In an earlier experimental study, lower rates of vascular endothelial growth factor (VEGF) were noted in animals with tumor

### Table I - Demographic characteristics and tumor histopathological findings.

<table>
<thead>
<tr>
<th>PJ(+) Anastomosis Leakage (n = 11)</th>
<th>PJ(–) Anastomosis Leakage (n = 53)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age in Years (range)</td>
<td>33</td>
<td>32.4</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>9/2</td>
<td>35/18</td>
</tr>
<tr>
<td>Tumor grade T1 T2 T3 T4</td>
<td>119-</td>
<td>35432</td>
</tr>
<tr>
<td>Lymph node involvement (–) (+)</td>
<td>38</td>
<td>2330</td>
</tr>
<tr>
<td>Disease Stage Stage I Stage II Stage III Stage IV</td>
<td>191-</td>
<td>6452-</td>
</tr>
</tbody>
</table>

### Table II - Comparison of long-term outcomes between groups.

<table>
<thead>
<tr>
<th>PJ(+) Leakage(n) 11</th>
<th>PJ(–) Leakage (n) 53</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LR(months, 95%CI)</td>
<td>33.9 (17.8-49.9)</td>
<td>44.7 (36-53.4)</td>
</tr>
<tr>
<td>OS (months, 95% CI)</td>
<td>19 (10.5-27.5)</td>
<td>28 (19.0-36.2)</td>
</tr>
</tbody>
</table>


RISULTATI: 44 pazienti erano di sesso maschile e 20 di sesso femminile; l'età media era di 61 anni (da 39 a 84). Del totale 11 pazienti hanno manifestato deiscenza della anastomosi PJ. La recidiva locale si è presentata in 5 (45,4%) di questi 11 pazienti, contro 4 recidive locali (7,5%) in pazienti che non hanno presentato deiscenza (p=0.02). La recidiva locale si è sviluppata prima nei pazienti con deiscenza rispetto a quelli senza (p=0.013). Al contrario non si sono rilevate differenze significative nella sopravvivenza libera da malattia o nella sopravvivenza complessiva.

CONCLUSIONE: La deiscenza dell'anastomosi PJ sembra essere associata ad una più frequente e più precoce recidiva locale, mentre non influenza la sopravvivenza.

Riassunto

INTRODUZIONE: A differenza dei pazienti con tumore del colon-retto, l'effetto sul tasso di sopravvivenza e recidiva della deiscenza anastomotica dopo intervento chirurgico per adenocarcinoma del pancreas non è chiaro. Il presente studio ha avuto come obiettivo di determinare le conseguenze della deiscenza della pancreato-digienne-stomia (PJ), in particolare sul tasso di recidiva locale e sul tempo stesso di recidiva, in pazienti sottoposti a duodenocefalopancreasectomia (DCP) per adenocarcinoma del pancreas.


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References


