

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



Ann. Ital. Chir., 2018 89, 4: 315-319
pii: S0003469X18028828

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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%¹⁻⁶ and 5%⁶⁻⁸, respectively. Pancreaticojejunostomy (PJ) leakage is

the most critical complication following PD, occurring in 12%-20% of patients^{9,10}. 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 cost¹¹. 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 outcomes¹².

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^{13,14}. Likewise, it was suggested that the presence of anastomotic leak increases secre-

Pervenuto in Redazione Maggio 2018. Accettato per la pubblicazione Giugno 2018

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tion of pro-inflammatory cytokines weakening cellular immunity and enhancing the growth of cancer cells that remain at the microscopic level¹⁵. However, a limited number of studies have reported contradictory effects of PJ leakage on recurrence¹⁶⁻¹⁸. 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 post-operative 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)¹⁰.

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.

Patients were classified into 2 groups: PJ(+) leakage group and PJ(-) leakage group. Statistical comparison of the 2 groups was performed using the Mann-Whitney U test for continuous variables, and Pearson's chi-square test, Fisher's exact test, and the Fisher-Freeman-Halton test for categorical variables. The factors affecting local recurrence were identified by using Cox regression analysis. The Kaplan-Meier test was used to analyze survival. Comparison of survival between the 2 groups was performed using the log-rank test. P value less than 0.05 accepted as statistically significant.

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

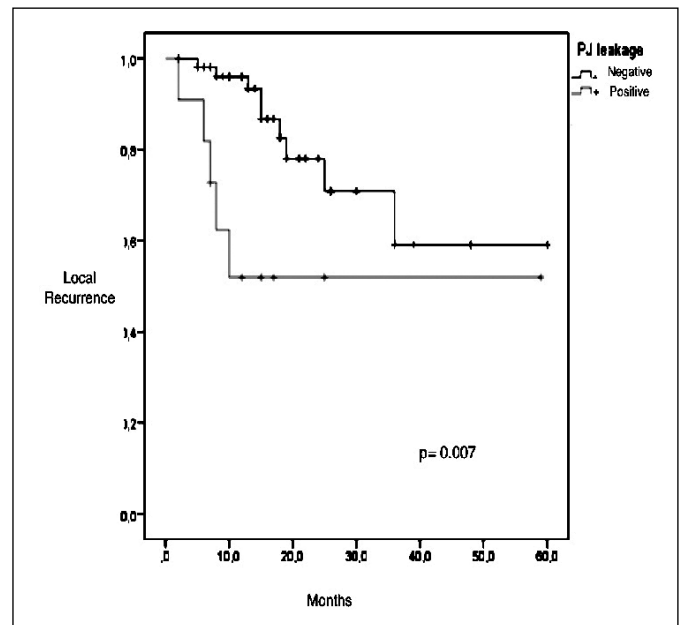


Fig. 1: Time to local recurrence in the patients with and without PJ leakage. PJ leakage was observed in 11 patients. Mean time to local recurrence was 32.8 months in the patients with leakage group (95% CI: 16.5-49.1), versus 54.3 months in those without leakage group (95% CI: 45.8-62.8) (P = 0.007).

TABLE I - Demographic characteristics and tumor histopathological findings.

| | PJ(+) Anastomosis Leakage (n = 11) | PJ(-) Anastomosis Leakage (n = 53) | P |
|---|---------------------------------------|---------------------------------------|-------|
| Median Age in Years (range) | 33 | 32.4 | 0.92 |
| Gender (M/F) | 9/2 | 35/18 | 0.48 |
| Tumor grade T1 T2 T3 T4 | 119- | 35432 | >0.99 |
| Lymph node involvement (-) (+) | 38 | 2330 | 0.5 |
| Disease Stage Stage I Stage II Stage III Stage IV | 191- | 6452- | >0.99 |

TABLE II - Comparison of long-term outcomes between groups.

| | PJ(+) Leakage(n) 11 | PJ(-) Leakage (n) 53 | P |
|---------------------|---------------------|----------------------|------|
| LR(months, 95%CI) | 33.9 (17.8-49.9) | 44.7 (36-53.4) | 0.01 |
| OS (months, 95% CI) | 19 (10.5-27.5) | 28 (19.9-36.2) | 0.18 |

one patient with grade B PF were conservatively followed-up. Additional percutaneous drainage procedures (abscess 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 metastasis²¹. 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 months¹⁶. 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

recurrence and no infection, as compared to the animals with tumor recurrence and infection. As a conclusion,, it was suggested that mediators released during the inflammatory process enhance VEGF, leading to an increase in angiogenesis and recurrence. It was also suggested that living tumor cells remain in the anastomosis line following gastrointestinal cancer surgery, and that the systemic inflammatory process is aggravated, proinflammatory cytokines are released, and the remaining tumor cells grow after anastomotic leak²⁵.

Radiotherapy is particularly effective in locoregional and recurrent disease treatment, as it provides local control of microscopic tumor cells. Patients with anastomotic leak is associated with longer length of hospital stay; thus, initiation of adjuvant chemoradiotherapy is delayed. In the present study, we think that delayed adjuvant treatment may be a factor that was associated with early development of local recurrence in the patients with anastomotic leak while disease stage was comparable between the groups. Nevertheless, groups did not differ significantly in terms of disease-free survival or overall survival. Moreover, the presence of lymph node involvement, poor differentiation, and perineural invasion were not associated with local recurrence, disease-free survival, distant metastasis, or overall survival.

Its retrospective nature and the limited patient number are the major drawbacks of this study. However, studying on single institutional data obtained from a specific patient population diagnosed with pancreatic adenocarcinoma gives this paper its clinical value.

In conclusion, PJ leakage was found to be associated with earlier and more frequent local recurrence in patients who underwent PD for PDA. The lack of a significant difference in the local recurrence rate between the present study's patients with and without PJ leakage might have been due to the limited number of patients included in the study. Interestingly, this study failed to show an association between the PJ leakage and survival. Additional prospective studies are needed to further clarify the effect of PJ leakage on survival and recurrence in pancreatic cancer patients.

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-digiunostomia (PJ), in particolare sul tasso di recidiva locale e sul tempo stesso di recidiva, in pazienti sottoposti a duodenocefalopancreasectomia (DCP) per adenocarcinoma del pancreas.

MATERIALIE METODI: Questo studio retrospettivo comprende 64 pazienti con adenocarcinoma del pancreas che

sottoposti a DCP tra Gennaio 2007 ed Agosto 2015. La deiscenza anastomotica della PJ è stata valutata sulla base dei criteri del Gruppo di Studio Internazionale della Fistola Pancreatica. Sono stati valutati gli effetti della deiscenza della anastomosi PJ sulla recidiva locale, sulla sopravvivenza senza malattia e sulla sopravvivenza complessiva.

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.

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

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