Surgical outcomes are hampered after endoscopic ultrasonography-guided ethanol lavage and/or Taxol injection in cystic lesions of the pancreas

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Research Article

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Abstract

Background and Aims

Endoscopic ultrasonography-guided ethanol lavage and Taxol injection (EUS-ELTI) in pancreatic cystic lesions have been recently performed in some medical centers. This study aimed to optimize the patient selection and analyze the outcomes in patients who underwent surgery after EUS-ELTI in pancreatic cystic lesions.

Methods

Among 310 patients who underwent EUS-ELTI between January 2007 and December 2014, 23 underwent surgery after EUS-ELTI owing to incomplete treatment and/or adverse events. We evaluated the surgical outcomes in patients who underwent surgery after EUS-ELTI. Then, we retrospectively compared the clinical outcomes of the patients who underwent the surgery after EUS-ELTI with those of patients who underwent upfront surgery for left-sided pancreatic lesions without the EUS-ELTI procedure.

Results

The pathology revealed degenerated cysts in 12 patients, mucinous cyst neoplasms in five patients, neuroendocrine tumors in two patients, and one intraductal papillary mucinous neoplasm (IPMN), one solid pseudopapillary tumor, one pancreatic ductal adenocarcinoma arising from an IPMN, and one hepatoid carcinoma. Twelve patients underwent laparoscopic distal pancreatectomy and five patients underwent open distal pancreatectomy. All six patients who had lesions in the pancreatic head underwent open pancreaticoduodenectomy. When we retrospectively compared the clinical outcomes between patients who underwent laparoscopic distal pancreatectomy after EUS-ELTI and those who did not receive the EUS-ELTI procedure, the spleen-preserving rate was 0% in the EUS-ELTI group and 61.7% (365/592) in the non-EUS-ELTI group ($P < 0.001$). Clinically relevant postoperative pancreatic fistulas occurred in 33.3% of patients in the EUS-ELTI group and in 6.8% of patients in the non-EUS-ELTI group ($P = 0.025$). The mean postoperative hospital stay was also shorter in the non-EUS-ELTI group than in the EUS-ELTI group (8.66 ± 5.66 and 13.56 ± 7.20, $P = 0.032$).

Conclusion

Surgical outcomes are compromised after EUS-ELTI in the cystic tumor of the pancreas. Further investigations are needed for investigation of the efficacy and safety of the EUS-ELTI procedure.

Introduction

With the widespread use of imaging modalities, cystic tumors of the pancreas are now detected more frequently and incidentally.[9] Surgical resection is the treatment of choice for cystic tumors due to the difficulty of differentiating between malignant and benign tumors at the initial diagnosis, and the inherent malignant potential of some cystic tumors. When a large cystic tumor is detected at the initial imaging evaluation or a size increase during the follow-up and suspicious findings of malignancy are detected, patients usually opt for surgical resection of the cystic lesion. However, for elderly patients, those who have numerous underlying conditions or ambiguous-sized cystic tumors, it is difficult to choose surgical resection as the initial treatment modality. Recently, endoscopic ultrasonography-guided ethanol lavage and Taxol injection (EUS-ELTI) in benign and low-grade malignant pancreatic cystic lesions have been performed in some medical centers and highlighted in gastroenterology journals.[4–6, 9, 16, 17] This procedure has merits, including being a minimally invasive procedure for patients with severe comorbidity and helping to increase the possibility of preserving the pancreatic parenchyma. Previous studies concluded that EUS-ELTI is safe and feasible, and in some cases, may bring a complete resolution of the disease.[3, 4, 6, 9, 10] Furthermore, some endoscopists expand the use of EUS-ELTI to the treatment of neuroendocrine tumors of the pancreas.[7, 11]

However, when adverse events occur after EUS-ELTI, or when the treatment results are unsatisfactory, patients are required to have a repeat procedure or undergo a surgical resection of the lesion. Although many reports on EUS-ELTI in pancreatic cystic tumors have shown various results, the surgical outcomes in patients who underwent surgery after the failure of EUS-ELTI have not yet been reported. Recently, minimally invasive pancreatic surgery has been increasingly accepted, especially in left-sided pancreatic resection, with superior results in terms of safety, hospital stay, and organ preservation compared with conventional open surgery.

In general, surgery after inflammation-inducing procedures is very complicated and results in various adverse events and unexpected damage to the patients. Acute pancreatitis or an inflammatory process after the EUS-ELTI procedure requires extensive resection of surrounding organs and may result in unexpected surgical adverse events. Assuming surgical outcomes of patients who underwent EUS-ELTI as the first-line treatment of pancreatic cysts are much worse than those of patients who initially underwent surgery, it is reasonable to establish a guideline for performing EUS-ELTI based not only on the tumor biology but also on the surgical outcomes of these patients.

With this assumption, we herein reported the surgical outcomes after the EUS-ELTI procedure for pancreatic cystic tumors and retrospectively compared the surgical outcomes with those of patients who underwent upfront surgery for the left-sided pancreatic lesions without the EUS-ELTI procedure during the same period. Comparisons for pancreatic head lesions were not performed since laparoscopic surgery for pancreatic head lesions is not yet accepted as a standard procedure.

Methods

The indications for EUS-ELTI were as follows: (i) unilocular or oligolocular cystic lesions (defined as having two to six locules within a cyst), (ii) indeterminate cystic lesions in which EUS-fine needle aspiration was indicated for obtaining additional information, and/or (iii) cystic lesions that increased in size during the observation period.[3, 9]

A total of 310 patients underwent EUS-ELTI between January 2007 and December 2014 at Asan Medical Center in South Korea. All EUS procedures were performed by experienced endosonographers and cyst fluid aspiration with ethanol lavage and/or Taxol injection procedures performed according to the regular treatment protocol. [9, 10] The 310 patients were followed for a median time of 48 months (Interquartile range [IQR] was 37.48 months). Among them, 209 patients had no evidence of disease recurrence over the median follow-up periods (49 patients were lost during follow-up among 209 patients) and 101 patients required additional treatments. Of the 101 patients, 63 were lost during follow-up and 15 underwent EUS-ELTI again without a recurrence of the disease. Twenty-three patients underwent surgery after EUS-ELTI, owing to incomplete treatment in the initial trial or the repeat trial of EUS-ELTI (n = 18), or adverse events after EUS-ELTI (n = 5). We analyzed the data of 23 patients who underwent surgery after EUS-ELTI (Fig. 1). The lesions of 7 patients were located on the pancreatic head, 5 were located on the pancreatic body, 8 were located on the pancreatic tail (Fig. 2). In addition, we compared the clinical outcomes between patients who underwent laparoscopic distal pancreatectomy (LDP) as an initial treatment and those who underwent LDP after EUS-ELTI, in terms of hospital stay, adverse events, operation time, and spleen preservation rate.

All statistical analyses were performed with IBM SPSS version 18.0 (IBM Corp., Somers, NY, USA). Categorical variables were analyzed using either the chi-square test or Fisher exact test, where appropriate. Parametric variables were analyzed using the Mann–Whitney test. A *P*-value of < 0.05 was considered statistically significant. The study was conducted in compliance with the ethical principles of the Declaration of Helsinki. The study protocol approved by the Institutional Review Board (IRB no. S2017-1136-0001) of the Asan Medical Center, and patients provided written informed consent. All methods were performed in accordance with the relevant guidelines and regulations.

Results

Demographics

The median age of the 23 patients was 60 years (IQR was 24 years), and 13 patients (56.5%) were women. The median body mass index (BMI) was 23.1 kg/m^2 (IQR was 4.45 kg/m^2) (**Table 1**). Fifteen patients received EUS-ELTI more than two times. Patients had various reasons for surgery: a size increase of the pancreatic lesion after EUS-ELTI in 13 patients, suspected malignancy in three patients, severe fluid collection around the pancreas after the procedure in one patient, massive portal vein thrombosis after EUS-ELTI with a cystic lesion in the pancreatic head in one patient, hematochezia after the procedure in one patient, progressive abdominal pain in one patient, and combined gastric surgery in one patient (**Table 2**).

The relation between the tumor location and the rate of conversion to surgical treatment was analyzed. After EUS-ELTI, among those who underwent surgery, 7 of 111 patients (6.3%) had lesions in the pancreatic head, 6 of 108 patients (5.6%) had lesions in the pancreatic body, and 8 of 81 patients (9.9%) had lesions in the pancreatic tail (**Table 3**). There were no statistically significant differences between tumor location and conversion rates to surgical treatment (p=0.560).

Perioperative outcomes

The mean operation time of the 23 patients was 279.4 min. The mean postoperative hospital stay was 14 days. Clinically relevant postoperative pancreatic fistulas (grade B and C, based on the International Society Grading for Pancreatic Fistula [ISGPF] system) occurred in six patients (26%) (**Table 1**). Among 23 patients who underwent surgery, 18 had severe adhesions and inflammation. Among 17 patients with left-sided pancreatic lesions, 12 patients underwent LDP (11 with combined splenectomy and one with spleen preservation) and five patients underwent open distal pancreatectomy. One patient underwent internal drainage (cystojejunostomy was performed because of severe adhesion from a previous operation and/or procedure); two years later, this patient underwent a pancreaticoduodenectomy because of abdominal pain induced by recurrent pancreatitis. The spleen preservation rate in patients with LDP after EUS-ELTI was 8.3% (1 of 12). All six patients who had lesions in the pancreatic head or uncinate process underwent an open pylorus-preserving pancreaticoduodenectomy (**Table 4**).

The pathologic outcomes of the 23 patients were reviewed. Twelve patients were reported to have pseudocysts or degenerated cysts, five patients with mucinous cyst neoplasms, and two patients with a neuroendocrine tumor. The remaining four patients were each reported as an intraductal papillary mucinous neoplasm (IPMN), a solid pseudopapillary tumor, a pancreatic ductal adenocarcinoma arising from IPMN, and a hepatoid carcinoma (**Table 5**).

We had concerns about the higher conversion rate to open laparotomy, the higher rate of adverse events, and the lower rate of spleen preservation in patients who underwent laparoscopic surgical resection after EUS-ELTI, especially in pancreatic tail lesions. Thus, we compared the clinical outcomes between patients who underwent LDP after EUS-ELTI and those who did not have the EUS-ELTI procedure for lesions in the pancreatic tail (control group, 592 patients) or the pancreatic body (146 patients) during the same period (**Tables6** and **7**). The mean tumor size, patient age, and patient BMI were comparable between the two groups.

No open distal pancreatic resections were performed in the control group. The spleen preservation rate was 0% (0 of 9) for patients in the EUS-ELTI group and 61.7% (365 of 592) for patients in the control group (P<0.001) with pancreatic tail lesions, 20% (1 of 5) for patients in the EUS-ELTI group, and 71.2% (104 of 146) for patients in the control group (P<0.05) with pancreatic body lesions. Clinically relevant postoperative pancreatic fistulas (grade B and C, based on the ISGPF system) occurred in three of nine patients (33.3%) in the EUS-ELTI group and in 40 of 592 patients (6.8%) in the control group (P=0.025) with pancreatic tail lesions. The mean postoperative hospital stay was also significantly shorter in the

control group than in the EUS-ELTI group (8.66±5.66 and 13.56±7.20, P=0.032) with pancreatic tail lesions.

Discussion

Recently, the results of EUS-ELTI have been reported in many papers. Although many advantages are expected from this procedure, some procedure-related adverse events and postprocedural inflammatory processes, including severe pancreatitis and severe inflammatory adhesions can develop on surrounding organs such as the stomach, colon, spleen, and blood vessels. These inflammatory processes make the subsequent surgery after EUS-ELTI treatment difficult, requiring extensive resection, disabling the preservation of the pancreatic parenchyma or adjacent organs. Finally, it makes it difficult to perform minimally invasive surgery. The advantages of minimally invasive laparoscopic pancreatectomy, such as distal pancreatectomy and pancreaticoduodenectomy for benign and low-grade malignant diseases, are well-known, including reports based on our center.[12, 14, 15] However, no study has been reported on the surgical outcomes after the failure of EUS-ELTI treatment.

Among the 23 patients who underwent surgical resection after EUS-ELTI treatment, 18 patients had operative findings of severe adhesion and inflammation. These findings made the operation difficult and caused many postoperative adverse events. In fact, almost all patients had procedure-induced pancreatitis and underwent open surgery for the treatment of lesions after EUS-ELTI. In general, pancreatic cystic tumors are usually suitable for minimally invasive surgery irrespective of the location of the lesions. Among the 23 patients in this series, however, only 12 patients (52.1%) could undergo laparoscopic surgery. In addition, all patients with pancreatic head lesions underwent an open pancreaticoduodenectomy. If patients chose surgical resection as the initial treatment of cystic tumors in the pancreas, they could undergo laparoscopic surgery in all cases, irrespective of the location of the lesion.

When distal pancreatectomy is performed in benign cystic lesions, spleen preservation is very important for the patient. The prevalence of overwhelming post-splenectomy infections in adults was reported to be 0.8–1.9%,[2] and this significant rate cannot be ignored, especially in old or immunocompromised patients. Many studies reported that spleen preservation decreased the rate of surgical site infection and improved short-term prognosis.[1, 13] In the present study, among 15 patients who underwent distal pancreatectomy (open or laparoscopic), the spleen could be preserved in only two patients (13.3%). Among 12 patients who underwent LDP, the spleen could be preserved in only one patient (8.3%). In our data on laparoscopic pancreatectomy, the spleen could be preserved in 72% (587 of 815) of the patients with benign pancreatic lesions. If the patients chose a minimally invasive surgery as the initial treatment, the spleen could have a higher chance of preservation.

Interestingly, in the present study, when the lesions were in the far tail of the pancreas, the possibility of additional surgery was higher (20%, 5 of 20) than when they were in other locations of the pancreas. This may have been due to the difficulty of accessing the lesions with EUS or the complicated vasculature

around the splenic hilum, possibly resulting in incomplete EUS-ELTI. There are many important structures around the head of the pancreas, including the portal vein and superior mesenteric vessels, and injuring these vessels during the EUS-ELTI procedure can lead to severe adverse events. Massive portal vein thrombosis developed after EUS-ELTI in one patient whose lesion was located in the pancreatic head, near the portal vein[8]. This study focused mainly on comparing the lesions in the body and tail of the pancreas; it obtained meaningful results since minimally invasive pancreatic resection of the pancreatic head lesion has not yet been accepted as a standard procedure. A comparative study of the lesions on the head of the pancreas will be conducted in the future.

Among the pathologic outcomes of 23 patients, two patients were diagnosed with cancer (8.7%). Among these two patients, one patient underwent EUS-ELTI to treat a neuroendocrine tumor, but the final pathology was hepatoid carcinoma. The other patient underwent EUS-ELTI to treat IPMN, but the final pathology was pancreatic ductal adenocarcinoma arising from IPMN with lymph node metastasis (One lymph node was reported as a metastatic lymph node among 11 harvested lymph nodes). Before performing EUS-ELTI, the initial diagnosis was always based on radiologic images. However, the initial diagnosis with radiologic images is not always precise, and an increased risk of oncologic safety can occur when the lesion includes malignancies like in this study.

Thus, an EUS guided chemo-ablation procedure should be considered very cautiously because of its suboptimal clinical data, often inaccurate of diagnosis, and compromised surgical outcomes. Although the present study has some limitations, including a small participant number, this study is significant because it is the first report presenting the surgical results after EUS-ELTI for physicians dealing with the endoscopic treatment of pancreatic cystic neoplasms.

In conclusion, surgical outcomes can be compromised or suboptimal after EUS-ELTI in pancreatic cystic tumors. Further investigations are needed for the efficacy and safety of the EUS-ELTI in the era of minimally invasive surgery.

Declarations

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Availability of data and materials

The datasets and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Authors' contributions

Main manuscript text was written by S.R.K and S.C.K. B.J.K and S.H.S prepared figures and tables. S.R.K carried out acquisition of data, statistical analysis, preparation of the manuscript and typing. K.B.S, K.M.P, D.W.H, J.H.L, Y.J.L and S.C.K participated in interpretation of data and critical revision. K.B.S and S.H.S participated in study coordination and its design. All authors read and approved the final manuscript.

Ethics approval and consent to participate

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. We clarify that informed consent was obtained from all of the included participants. The study protocol approved by the Institutional Review Board (IRB no. S2017-1136-0001) of the Asan Medical Center, and patients provided written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Due to technical limitations, table 1 to 7 is only available as a download in the Supplemental Files section.

Figures

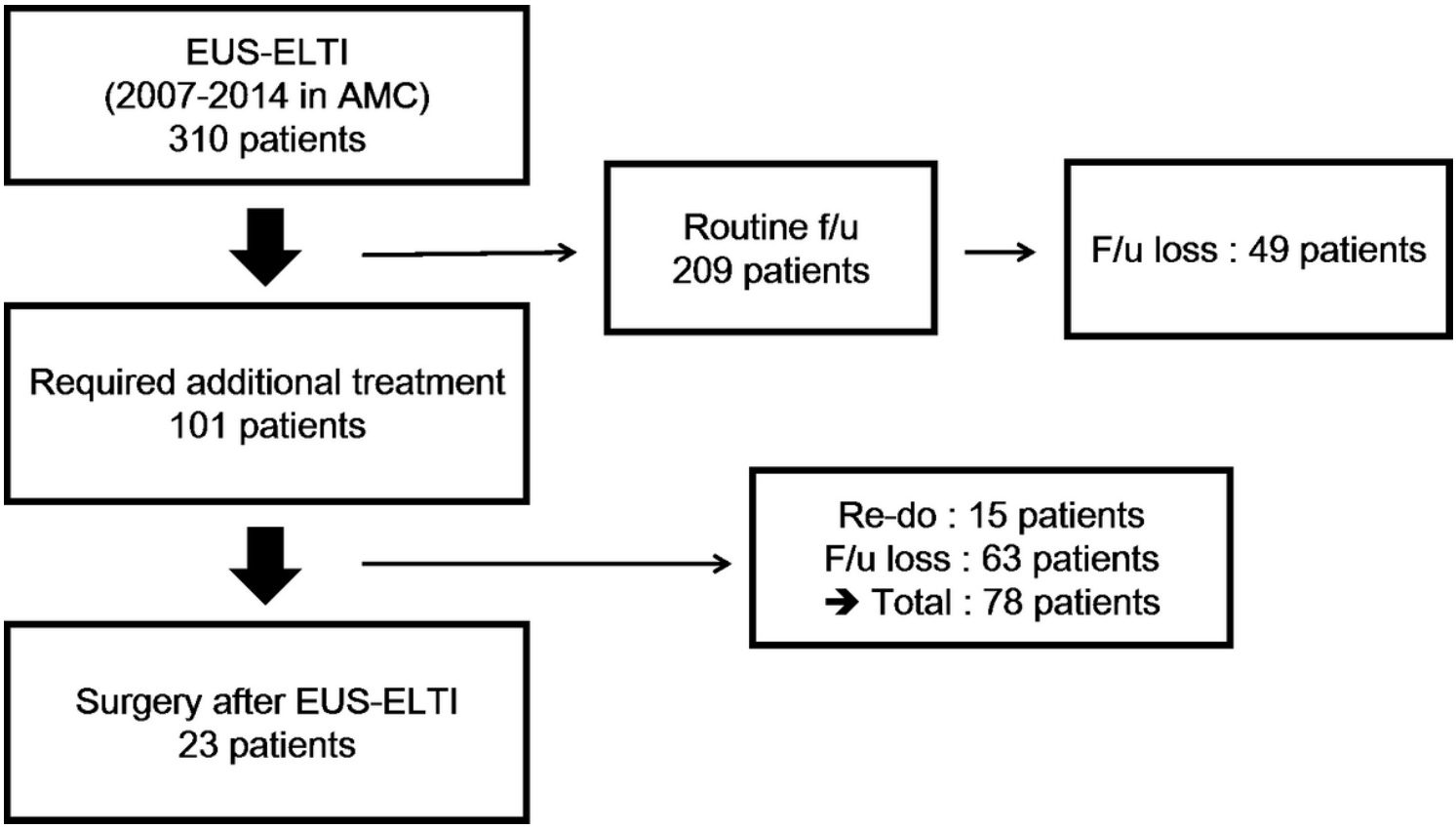

Figure 1

Study flow diagram

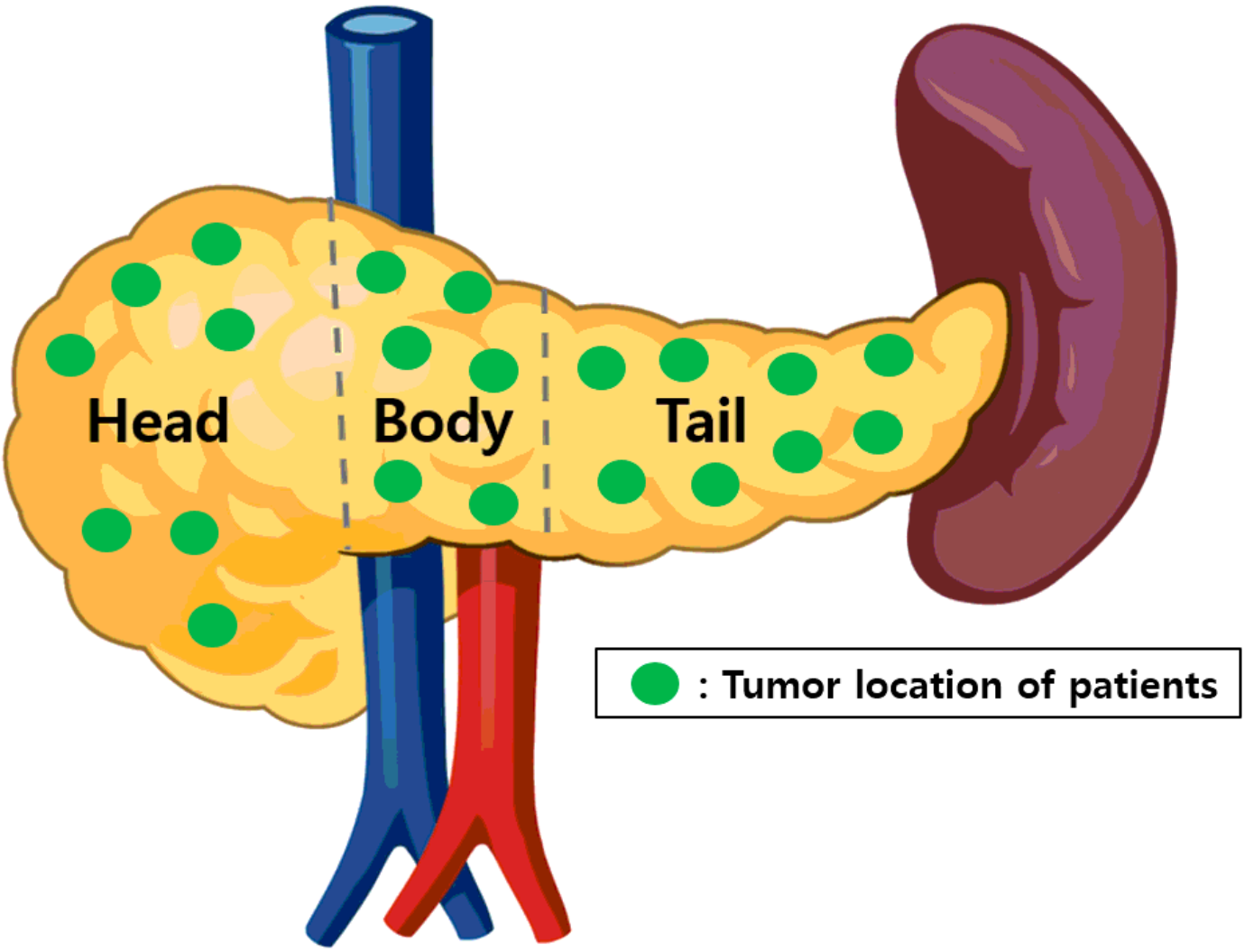

Figure 2

Distribution of tumor location

Supplementary Files

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- Table1.Patientdemographicsandperioperativeoutcomes.tif
- Table2.Reasonsforsurgery.tif
- Table3.Locationaldistribution.tif
- Table4.Operationmethods.tif
- Table5.Pathologicoutcomes.tif

- Table6.ComparisonofbodylesionsinLDP.tif
- Table7.ComparisonoftaillesionsinLDP.tif