Pathologic findings of pancreatoduodenectomy resection specimens: A six-year review of 78 cases at King Hussein Medical Centre

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ABSTRACT

Objectives: To analyse the different histopathological findings, we encounter in Whipple pancreatoduodenectomy resection specimens in relation to age, gender and the histopathologic parameters of the tumours.

Patients and methods: Data from a case series of consecutive patients who underwent Whipple pancreatoduodenectomy specimen histopathology were retrospectively reviewed and analysed between January 2015 and February 2020.

Results: A total of 78 patients underwent the classical Whipple procedure at King Hussein Medical Centre (KHMC), including 47 males and 31 females (M:F ratio 1.5). The mean age was 58.6 (19-83) years. Six patients underwent pancreatoduodenectomy as a treatment for chronic pancreatitis and the remaining 72 patients underwent pancreatoduodenectomy for presumed or proven malignancy by radiological (MDCT/MRI) or by CT-FNA biopsy. Fifteen patients (19.2%) had benign pancreatic lesions (including the 6 patients underwent pancreatoduodenectomy for chronic pancreatitis) and 63 (80.8%) patients had malignancy in the overall specimen (n=78). Nine patients (12.5%) had benign pathology and 63 (87.5%) patients had malignancy from the presumed or proven malignancy specimen (n=72).
Patients with benign pathology were more commonly female. The most common pathologic stage of the tumours was T3 (57.1%). Regarding tumour differentiation, (76.2%) were moderately differentiated. Mean tumour size was 3.58 cm. surgical margins were evaluated in all specimens. The margin was involved in 11.1% of the specimens. Perineural invasion present in 76.2% of all specimens while lymphovascular invasion was present in 52.4% of the specimens. Thirty-three (52.4%) specimens showed lymph node metastasis.

Conclusion: Several factors need to be evaluated during the histopathologic assessment of surgical specimen of pancreatoduodenectomy (Whipple resection), these factors include the histopathologic type of the tumour, the size of the tumour, tumour extension, tumour location, surgical margin status, lymphovascular or perineural invasion, and lymph node status. The need for more thorough and accurate assessments of the evolution of patients with suspected malignant lesions, in particular earlier diagnosis and management as most of the patients diagnosed at advanced stages. Number of involved lymph nodes by metastasis and lymph node ratio should be considered in final pathological reports due to high prognostic value. Benign pathology in a presumed malignancy should be considered in a resected specimen even with radiological signs suggestive of malignancy.

Keywords: Whipple procedure, pancreatoduodenectomy, pancreatic ductal adenocarcinoma, ampullary carcinoma, periampullary carcinoma.

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Introduction

Pancreatoduodenectomy (Whipple procedure) is a major surgical procedure involving resection of the head of the pancreas, duodenum, bile duct, and gall bladder, with or without distal portion of the stomach (pylorus preserving pancreatoduodenectomy).

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The Whipple procedure is one of the most complex surgeries performed for the management of many malignant and benign indications, including a variety of tumours involving the head of the pancreas, ampullary and periampullary tumours, common bile duct and duodenal tumours. It is also performed in benign neoplasms mimicking malignancy (mucinous cystadenoma, serous cystadenoma, pancreatic pseudocyst) and in chronic pancreatitis. Other rare indications include complex pancreatic and duodenal trauma. However, pancreatic head cancer is the most common indication for the Whipple procedure.
There are two types of Whipple procedure, i.e. the classical Whipple procedure named after the American surgeon Allen Oldfather Whipple (1881-1963) and the pylorus-preserving Whipple procedure, which was initially adapted as an alternative to the classical Whipple procedure in the setting of chronic pancreatitis (1). The classical Whipple involves resection of the head of the pancreas, duodenum, bile duct, gall bladder, and a portion of the stomach, followed by restoration of the flow of the gastrointestinal tract by reconnection of the remaining portions of the pancreas, bile duct, and stomach to the small intestine. In a pylorus-preserving Whipple procedure, the stomach portion is not resected and is connected directly to the small intestine.

Pancreatic cancer is the 11th most common cancer in the world, with 458,918 new cases and 432,242 deaths (4.5% of all deaths caused by cancer) in 2018 (2), The vast majority of pancreatic cancers involve the head of the pancreas 60-70%, while 20-25% are located in the body and tail and 10-20% of carcinomas involving the whole organ (3). Only 15-20% of patients with pancreatic head cancer present with resectable disease and are amenable to the Whipple procedure (4).

Pancreatic ductal adenocarcinoma (PDAC) is by far the most common histologic type of primary malignant neoplasm of the pancreas and accounts for more than 85% of pancreatic cancers. The remaining pancreatic cancers are rare and include solid pseudo papillary neoplasms (SPN), neuroendocrine tumours (NET), and acinar cell carcinoma (5).

The pathologic assessment of pancreatoduodenectomy specimens needs a thorough evaluation of several histopathologic factors. These histopathological factors provide clinicians with powerful prognostic indicators and guide the clinician to accurate therapeutic decisions. These factors include the histopathologic type of the tumour, the size of the tumour, tumour extension, tumour location, surgical margin status, lymphovascular or perineural invasion, and lymph node status.

METHODS

This is a retrospective case series of consecutive patients who underwent pancreatoduodenectomy resections in King Hussein Medical Centre between January 2015 and February 2020. All specimens received in the department of Pathology for both the malignant and non-malignant indication was retrieved and included in the study. details of diagnosis and staging were evaluated from all specimen records including the histopathologic diagnosis, tumour type, the size of the tumour, tumour grade, tumour extension, tumour location, surgical margin status, lymphovascular or perineural invasion, and lymph node status. The TNM staging of Tumors based on AJCC classification (7th and 8th edition).

RESULTS

Between January 2015 and February 2020, a total of 78 patients underwent the classical Whipple procedure at King Hussein Medical Centre (KHMC), including 47 males and 31 females (M:F ratio 1.5), The mean age was 58.6 (19-83) years. Patients with benign pathology were more commonly female. The perioperative mortality rate (30-day mortality) was 3.8%, all of the death cases occur in patient with proven malignancy by definitive histopathological results. It was greater in patients older than age 70 years and occur in the early cases of our series. The complication rate was 58%, the most common complication was surgical site infection, Intra-abdominal infection, postoperative pancreatic fistula and Delayed gastric emptying. Most of the complication occur in patient with poor preoperative nutritional status, patient with more than one comorbidity (Diabetes, coronary artery disease and renal impairment), and patients with preoperative biliary drainage. The complication rate was more common in patients with malignancy, probably because they were older patients, had poor nutritional status and more comorbidity. Six patients underwent pancreatoduodenectomy as a treatment for chronic pancreatitis and the remaining 72 patients underwent pancreatoduodenectomy for presumed or proven malignancy by preoperative clinical, radiological, or histopathological diagnosis. None of the six patients underwent pancreatoduodenectomy as a treatment for chronic pancreatitis found to harbour malignancy. Nine patients (12.5%) had benign pancreatic lesions and 63 (87.5%) patients had malignancy from the presumed or proven malignancy specimen (n=72). The most common benign pathology among those with presumed or proven malignancy was chronic pancreatitis 3/9 (33.3%), while three (33.3%) were Intraductal papillary mucinous neoplasms (IPMN), two (22.2%) were pancreatic mucinous cystadenoma, and one (11.1%) was an ampullary adenoma with low grade dysplasia. Thirty-six (87.5%) patients had malignancy; of these, 32 (50.8%) patients had pancreatic ductal adenocarcinoma (PDAC), 15 (23.8%) had ampullary carcinoma (AC), six (9.5%) had periampullary carcinoma (PAC), four (6.3%) had cholangiocarcinoma (CC), three (4.8%) had solid pseudo papillary tumours (SPT), two (3.2%) had pancreatic mixed adenoneuroendocrine carcinoma (PMANEC), and one (1.6%) had a pancreatic neuroendocrine tumour (PNET). ***(Table I) (Figure 1).***

The most common pathologic stage of the tumours was T3 (57.1%), followed by T2 (27%), T1 (12.7%) and T4 (3.2%) tumours. Regarding tumour differentiation, seven (11.1%) were of well differentiated tumours, 48 (76.2%) were of moderately differentiated tumours and eight (12.7%) were of poorly differentiated tumours. Mean tumour size was 3.58 cm (range from 1-9 cm). Surgical transection margins were evaluated in all specimens. Stomach cut margins, jejunal resection margins, and common bile duct margins were free of tumour in all specimens, while the pancreatic cut margin (which includes the posterior pancreatic surface, anterior pancreatic surface, PV/SMV groove margin, and SMA margin) was involved in 7/63 (11.1%) of the specimens (six with PDAC and one with CC). The posterior margin was involved in six cases and the SMA margin was involved in one case. Perineural invasion was present in 76.2% of all specimens, while lymphovascular invasion was present in 52.4% of specimens. Thirty-three (52.4%) specimens showed lymph node metastasis (21 cases had PDAC, five had ampullary adenocarcinoma, two had periampullary adenocarcinoma, three had cholangiocarcinoma, and two had pMANEC) ***(Table II).***

Table I. Histopathological diagnosis of the pancreatoduodenectomy specimens (n=78)

Histopathological diagnosis in patient with chronic pancreatitis (n=6)		
	N	**Percent**
Chronic pancreatitis	6	100%
Histopathological diagnosis in patient with presumed or proven malignancy		
	N	**Percent**

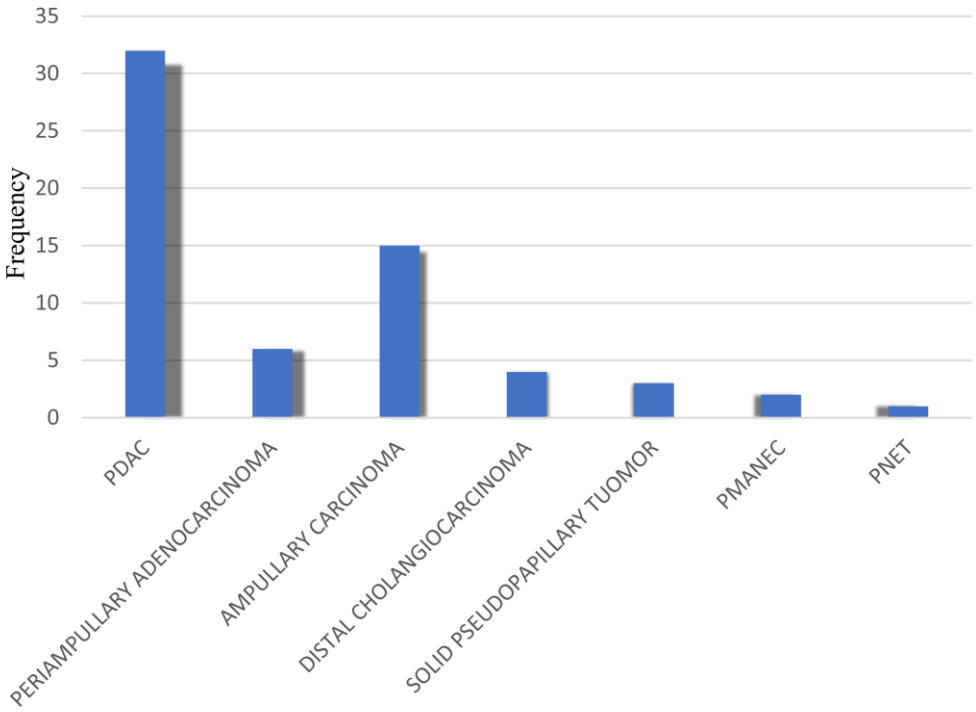
BENIGN LESIONS	n=9	12.5
Chronic pancreatitis	3	33.3
Intraductal papillary mucinous neoplasms (IPMN)	3	33.3
Pancreatic mucinous cystadenoma	2	22.2
Ampullary adenoma	1	11.1
MALIGNANT LESIONS	n=63	87.5
Pancreatic ductal adenocarcinoma (PDAC)	32	50.8
Periampullary carcinoma (PC)	6	9.5
Ampullary carcinoma (AC)	15	23.8
Cholangiocarcinoma (CC)	4	6.3
Solid pseudopapillary tumour (SPT)	3	4.8
Pancreatic mixed adenoneuroendocrine carcinoma	2	3.2
Pancreatic neuroendocrine tumor	1	1.6

Table II. Detailed pathological findings of malignant pancreatoduodenectomy specimens

	N=63 and percentage
Mean age	58.6 (19-83) years
Gender (M:F ratio)	1.5
Pathological stage	
T1	8 (12.7%)
T2	17 (27.0%)
T3	36 (57.1%)
T4	2 (3.2%)
Tumour differentiation	
Well differentiated tumours	7 (11.1%)
Moderately differentiated tumours	48 (76.2%)
Poorly differentiated tumours	8 (12.7%)
Mean tumour size	3.58 cm (range 1-9 cm)
Perineural invasion	48 (76.2%)
Lymphovascular invasion	33 (52.4%)
Positive surgical margin (R1)	7 (11.1%)
LNs metastasis	33 (52.4%)
Pancreatic ductal adenocarcinoma	21/33 (33.6%)
Ampullary adenocarcinoma	5/33 (15.2%)
Periampullary adenocarcinoma	2/33 (6.1%)

Cholangiocarcinoma	3/33 (9.1%)
Pancreatic mixed adenoneuroendocrine carcinoma	2/33 (6.1%)

Figure 1: Pathological diagnosis



PDAC: Pancreatic ductal adenocarcinoma, PMANEC: Pancreatic mixed adenoneuroendocrine carcinoma, PNET: Pancreatic neuroendocrine tumor

DISCUSSION

Classical Whipple pancreatoduodenectomy procedure is the standard of practice at our institution, this is probably due to the surgeon's preference and the high incidence of delayed gastric emptying (DGE) observed in patients undergoing pylorus-preserving pancreatoduodenectomy in several studies, without significant differences in the oncologic outcome and mortality in both techniques.

The prevalence of benign disease ranging from 8-15.6% in patients who underwent pancreatoduodenectomy procedure for malignancy (6-8). Foroughi et al. reported the 13.7% of the histology samples obtained after Whipple resection are benign (6). Kavanagh et al. reported that 8% of 112 patients who underwent the Whipple procedure had benign disease (7). Others showed a prevalence of benign disease in patients who underwent pancreatoduodenectomy for presumed malignancy of 15.6% (8). Yeo reported a higher prevalence of 32% in specimens with various benign pancreatic lesions (9). Shyr et al. reported two cases of benign lesions including a cholesterol polyp in the distal common bile duct and an ampullary intramural ectopic gland hyperplasia in final pathological specimens obtained for suspected pancreaticobiliary cancer (10). Kennedy et al., reported that (12.9%) of patients that underwent pancreatoduodenectomy surgery had benign findings in the final pathological diagnosis, even with a

mass lesion present in 67%, 71%, and 67% of patients in CT scan, MRI and EUS, respectively, they concluded that the uses of theses imagining modalities are accurate in differentiation of resectable form unresectable disease but not accurate in differentiation of benign from malignant pancreatic diseases (11). Shrikhande SV et al., reported benign disease in 6.5 % after pancreatoduodenectomy for presumed malignancy, at the same study they found that radiological signs (except the double duct sign) suggestive of malignancy were seen in more than 50% of the benign cases and they conclude that no investigation can reliably discriminate benign from malignant in a small subset of benign pathologies (12).

Concerning preoperative pathology, Studies show that preoperative biopsy is limited by sampling errors due to the morphology of pancreaticobiliary cancers, this include tumors with extensive desmoplastic reaction seen in pancreatic ductal adenocarcinoma, small tumor, as well as interpretative errors in differentiated carcinomas with minimal cytological abnormality from other tumors such as mucinous or Intraductal papillary tumors. Another limitation of preoperative biopsy is the complications associated with pancreatic cancer biopsy, which may range from simple self-limiting mild pancreatitis to tumor cell seedling. Currently a preoperative pathologic diagnosis is indicated in patients with borderline or unresectable lesions prior to neoadjuvant therapy, in the presence of metastatic disease and in cases of undetermined etiological diagnosis (13,14). In our series, benign disease found in 9 of 72 (12.5%) specimens from those with preoperative presumed or proven malignancy. Variations in the prevalence of benign lesions is mainly due to the difficulty in differentiating of some benign lesions from malignant lesions, as unusual pathological lesions may still mimic malignant conditions leading to a Whipple resection despite recent advances in diagnostic imaging. Our practice is to go for pancreatoduodenectomy when clinically and radiologically resectable pancreatic cancer is suspected and biopsy in case of neoadjuvant, palliative chemotherapy is to be administered, or when undetermined pathology is present.

Tumour pathological stage (T) has been identified as a prognostic factor in many series in pancreatic cancer. In our series, 60.3% of the specimens showed an advanced pathological stage (T3 and T4), Foroughi et al. and Goret et al. also reported that most of their cases were in an advanced stage (6,15). This emphasizes the need for more thorough and accurate assessments of the evolution of patients with suspected malignant lesions, in particular earlier diagnosis and management. However, these tumours are mostly asymptomatic in the early stages of the disease and, consequently, the majority of patients with malignant lesions present late in the disease course with locally advanced and unresectable tumours.

The overall survival (OS) among patients with positive surgical margins is poor, and patients with tumour- free resection margins have better survival (16,17). Esposito et al. and Pandey defined R1 as a tumour 1 mm from the resection margin (18). Esposito and Khalifa et al. consider the resection margin as positive when tumour cells have reached the inked margin (19). A recent analysis of surgical resection margins by Osipov et al. showed that a 2 mm positive margin is an independent predictor of local recurrence-free survival (20). Other studies have reported that resection margin status is not an independent risk factor for overall or disease- free survival. Variations in these results are probably due to the lack of standardized pathological definitions for resection margin status (21). In our study, seven (11.1%) cases (six PDAC, one CC), the surgical margin was positive (R1), of these, the tumour was adjacent to the posterior surgical margin in six specimens and at the SMA margin in one case. The reported R1 resection rates after pancreatoduodenectomy vary from 14% to 76%. Takahashi et al., report R1 in 7.9% of the cases when R1 (more than 1-mm) and 47.8% (when R1 defined as resection margin distance of 1 mm or less) in the 8 surgical resection margins used in their pathology protocol. Winter et al., report that 42% had positive margins status in the largest single-institution experience with 1423 pancreatoduodenectomy for pancreatic cancer. large variation is the result again of a lack of standardization of the definition of positive surgical margins and variations in the definition of resectability in cases with aggressive disease in different series (22,23).

Like many other case series, in our specimens, the tumours were mostly moderately differentiated (59.1%), with 11.1% and 12.7% well and poorly differentiated tumours respectively (24,25).

Lymph node status is one of the most important independent prognostic factors of recurrence and survival, in particular in patients undergoing resection for pancreatic cancer. Several studies now support that the number of lymph node involvement along with the lymph node ratio (LNR) also as an independent prognostic factors in pancreatic cancer (26,27,28). due to these prognostic values, the Eighth Edition of the American Joint Committee on Cancer (AJCC) recently revised the N stage, and subdivided the N1 stage from the seventh edition (N0: no regional LN metastasis and N1: regional LN metastasis) into N1 and N2 according to the number of positive regional lymph nodes (N0: No regional lymph node metastasis, N1: Metastasis in 1-3 regional lymph nodes, N2: Metastasis in ≥4 regional lymph nodes). Furthermore, the lymph node ratio (the number of positive lymph nodes/total number of lymph nodes) significantly correlated with worse survival when LNR > 0.2 in several studies (29). The true incidence of lymph node metastasis varies, this is perhaps due to the variability in tumor types, tumor stage in the pancreatoduodenectomy specimens, and whether the patients received neoadjuvant chemotherapy or not. Another reason is the inadequate lymphadenectomy which may result in underestimation of the N stage. A recent Population Study Using the US Surveillance, Epidemiology and End Results (SEER) showed that more than 50% of the patients undergoing pancreatoduodenectomy received inadequate lymphadenectomy. However, Lymph node metastasis pathologically confirmed in around two third of the cases (30). Kanda et al., reports pathologically confirmed lymph node metastasis in (67.4%) of the cases (31). Dhakhwa R., report (54.8%) lymph node metastasis in his series (19), others report higher incidence of lymph node metastasis (32,33,34). In our review, we found that 33 (52.4%) of specimens had lymph node metastasis. The number of involved lymph nodes ranged from 1 to 10 lymph nodes.

Perineural invasion (PNI) and lymphovascular invasion are established prognostic factors in pancreatic ductal adenocarcinoma (PDAC), cholangiocarcinoma and other periampullary tumours. Several studies have shown that perineural invasion (PNI) and lymphovascular invasion are associated with a poor outcome (35,36,37).

CONCLUSION

Several factors (include the histopathologic type of the tumour, the size of the tumour, tumour extension, tumour location, surgical margin status, lymphovascular or perineural invasion, and lymph node status) need to be evaluated during the histopathologic assessment of surgical specimens from pancreatoduodenectomy (Whipple resection). The need for more thorough and accurate assessments of the evolution of patients with suspected malignant lesions, in particular earlier diagnosis and management as most of the patients diagnosed at advanced stages. A standardized protocol to define surgical margins is needed to allow comparative studies from different institutions and for optimizing the treatment strategies for pancreatic cancer. Number of involved lymph nodes by tumor and LNR should be considered in final pathological reports due to high prognostic value. Benign pathology in a presumed malignancy should be considered in a resected specimen even with radiological signs suggestive of malignancy. Surgeons and pathologists should be aware of these factors and other features that may affect patient prognosis and survival.

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