



## Histopathologic Analysis of Pancreaticoduodenectomy Specimen

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### ABSTRACT

**Introduction:** Whipple's Pancreaticoduodenectomy has increasingly been used as an appropriate resectional procedure for tumors of the periampullary region which are pancreatic, periampullary, ampullary and biliary tumors. Our aim was to study the distribution and histopathologic features of these tumors and to examine local trends of periampullary neoplasms resected with a PD.

**Methods:** A descriptive study was conducted in the department of Pathology, Kathmandu Medical College Teaching Hospital from July 2013 to June 2016.

**Results:** Thirty five patients underwent Whipple's Pancreaticoduodenectomy procedure during a period of 36 months from July 2013 to June 2016. Malignant tumor was present in 31 (88.57%) cases where as four cases (11.43%) harboured benign lesions. Periampullary mixed carcinoma was the predominant tumor (34.28%) followed by periampullary duodenal (20%), ampullary (14.28%), pancreatic adenocarcinoma (11.42%) and distal cholangiocarcinoma (5.71%). There was no significant difference in tumor size among periampullary, ampullary, pancreatic and biliary carcinomas. Ampullary carcinomas were predominantly well differentiated (80%) where as the other tumors were mostly moderately differentiated. Lymphovascular and perineural invasion varied in different tumor types. Four pancreatic adenocarcinomas showed lymphovascular and perineural invasion. Adequate surgical margin clearance was achieved in most of the cases except in one case each of periampullary duodenal carcinoma and distal cholangiocarcinoma and two cases of pancreatic adenocarcinoma..

**Conclusions:** Pancreaticoduodenectomy specimen requires thorough histopathological evaluation. Pathologists should also be aware of possibility of a benign diagnosis in PD specimens which have been resected presuming malignancy based on clinical judgement and radiological data.

**Keywords:** *histopathologic evaluation, pancreaticoduodenectomy, periampullary carcinoma.*

### INTRODUCTION

Kausch is credited with the first successful resection of the duodenum and portion of pancreas (pancreaticoduodenectomy) which was later popularized by Whipple and now bears his name for the operation.<sup>1,2</sup> Advances in surgical technique, perioperative care and concentration of surgery in large volume centres have significantly improved mortality and morbidity associated with the Whipple's procedure.<sup>3,4</sup> Today Whipple's Pancreaticoduodenectomy has increasingly

been used as a safe and appropriate resectional option for tumors of the periampullary region which are pancreatic, ampullary, biliary and duodenal tumors.<sup>1,5</sup>

The distribution of resected pancreatic, ampullary, biliary and duodenal carcinomas is variable in different

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studies which affects patient survival. A recent large study done by Chen et al. on 501 periampullary cancers found ampullary carcinomas represented the majority of cancers subjected to a pancreaticoduodenectomy while other literature show pancreatic cancer to be more frequent.<sup>6,7</sup> Pathologic assessment of surgical specimens from PD needs special attention in order to accurately evaluate many factors that are prognostically important. These factors include tumor location, extension, size, surgical margin status, vascular or perineural invasion and lymph node status.<sup>8-10</sup>

The aim of this study was to examine the distribution and histopathologic features of pancreatic, ampullary, biliary and duodenal cancers resected by PD in a tertiary level hospital over a period of three years.

## METHODS

A descriptive study was conducted in the department of Pathology, Kathmandu Medical College Teaching Hospital from July 2013 to June 2016. Pancreaticoduodenectomy specimens received in the department of Pathology for various clinical indications were included in the study. The specimens were fixed in 10% formalin, grossed and processed as per standard protocol. Location of the tumor, histopathologic categorization, grading, lymphovascular and perineural invasion, margin status and lymph node status were assessed. TNM staging of the tumor was done based on AJCC TNM classification.<sup>11</sup> Relevant clinical history and radiological findings were traced where applicable.

## RESULTS

Thirty five patients underwent Whipple's Pancreaticoduodenectomy procedure during a period of 36 months (July 2013 to June 2016). Nineteen (54.3%) patients were male and 16 (45.7%) were female. The mean age of the patient was 60.45 years (range: 36 to 77 years). Fifteen of the patients (42.8%) belonged to 61-70 age group (Table 1). Most of the patients presented with history of jaundice.

**Table 1. Agewise distribution of patients undergoing Pancreaticoduodenectomy.**

Age (years)	n (%)
30-40	2 (5.7)
41-50	3 (8.6)
51-60	9 (25.7)
61-70	15 (42.8)
71-80	6 (17.2)

Among the thirty five PD specimens, malignant tumor

was present in thirty one (88.57%) cases where as four cases (11.43%) harboured benign lesions. Periampullary mixed carcinoma was the predominant tumor (34.28%, figure 1) followed by periampullary duodenal (20%), ampullary (14.28%, figure2), pancreatic adenocarcinoma (11.42%, figure3) and distal cholangiocarcinoma (5.71%). One of the cases which was clinically diagnosed as a pancreatic malignancy turned out to be Neuroendocrine tumor (2.85%, figure4) on histopathologic examination and was confirmed by Immunohistochemistry. One case which was suspected of periampullary malignancy was found to be Periampullary adenomatous hyperplasia (2.85%) and another case suspected of distal cholangiocarcinoma did not reveal any neoplastic lesion and showed non-specific inflammation (2.85%) only. Two cases which were diagnosed as Mucinous cystadenoma on radiological examination were found to be Serous cystadenoma (2.85%) and Non invasive Mucinous cystic neoplasm with low grade dysplasia (2.85%) respectively on histopathologic examination. (Table 2)

Table 2. Histopathologic Diagnosis of Pancreaticoduodenectomy specimen.	
Diagnosis	n(%)
Malignant lesions	31 (88.57)
Periampullary duodenal carcinoma	7 (20)
Periampullary mixed	
Mixed exophytic	8 (22.85)
Mixed ulcerative	4 (11.42)
Ampullary carcinoma	5 (14.28)
Distal cholangiocarcinoma	2 (5.71)
Pancreatic ductal adenocarcinoma	4 (11.42)
Pancreatic Neuroendocrine tumor	1 (2.85)
Benign lesions	4 (11.42)
Pancreatic Serous cystadenoma	1 (2.85)
Non invasive Mucinous cystic neoplasm with low grade dysplasia	1 (2.85)
Periampullary adenomatous hyperplasia	1 (2.85)
Non specific inflammation	1 (2.85)

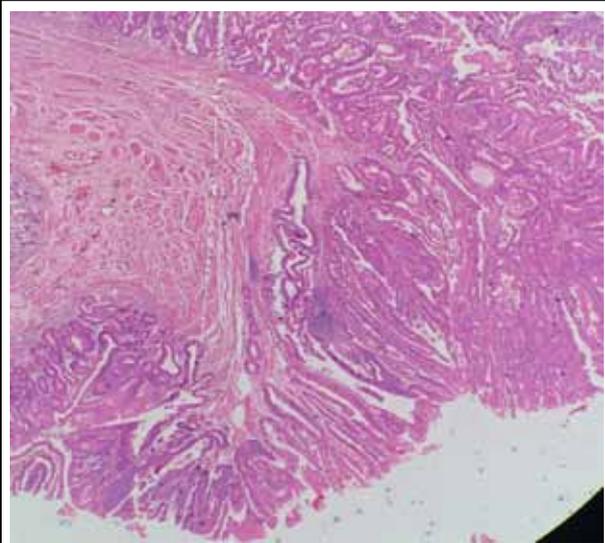


Figure 1. 40x H&E periampullary mixed carcinoma.

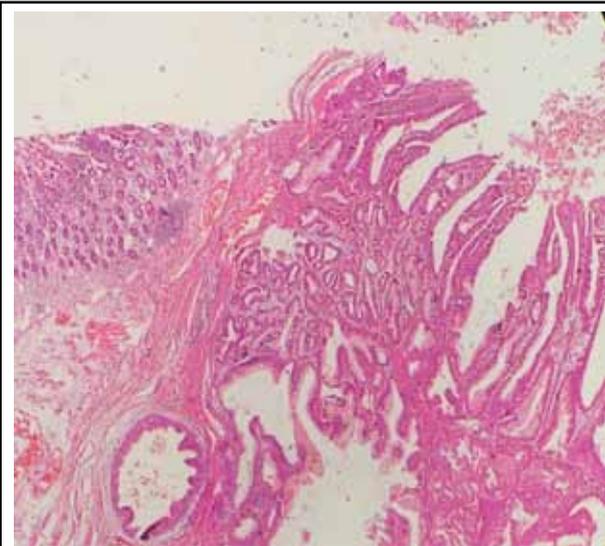


Figure 2. 100x H&E Ampullary carcinoma.

Maximum tumor dimension, tumor differentiation, mean number of lymph node dissected, lymph node status, resected margin status, lymphovascular and perineural invasion among the different adenocarcinomas are demonstrated in Table 3. Most of the periampullary mixed and duodenal, pancreatic and distal cholangiocarcinomas were moderately differentiated whereas ampullary carcinomas were predominantly well differentiated (80%). There was no significant difference in tumor size among periampullary, ampullary, pancreatic and biliary carcinomas. Lymphovascular and perineural invasion varied in different tumor types. Surprisingly all four pancreatic adenocarcinomas showed lymphovascular and perineural invasion. The average number of lymph nodes dissected was twelve.

The lymph node involvement by tumor varied in different tumor types. Lymph nodes were involved by tumor in all the four cases of Pancreatic adenocarcinoma (100%). Adequate surgical margin clearance was achieved in most of the cases except in one case of periampullary duodenal carcinoma and two cases of pancreatic adenocarcinoma. Pathologic staging of the malignant tumors is demonstrated in Table 4.

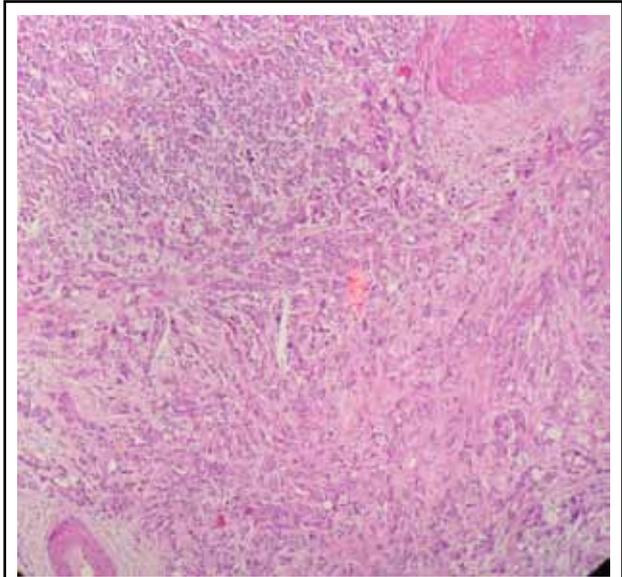


Figure 3. 100x H&E Pancreatic adenocarcinoma.

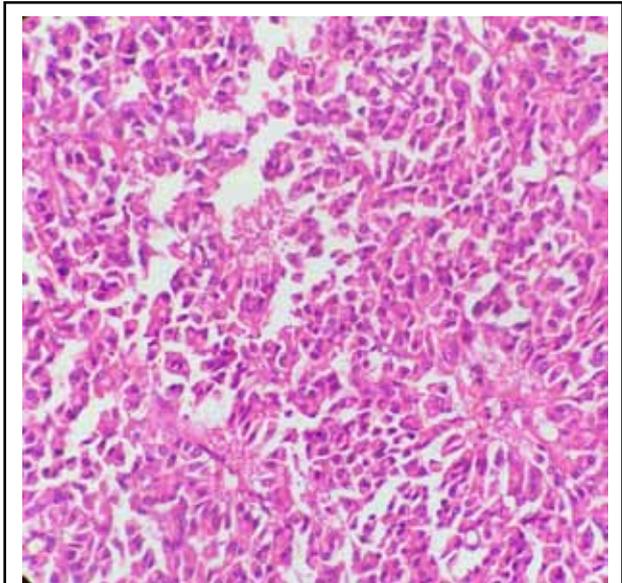


Figure 4. 400x H&E Neuroendocrine tumor.

**Table 3. Histopathologic findings of adenocarcinoma in Pancreaticoduodenectomy specimen.**

	Periampullary duodenal carcinoma (n = 7)	Periampullary mixed carcinoma (n = 12)	Ampullary carcinoma (n = 5)	Distal cholangiocarcinoma (n = 2)	Pancreatic adenocarcinoma (n = 4)
Tumor diameter (cm)					
Mean	3.1	3.3	2.2	3.5	3.2
Range	1.2-7	1.3-8	1.5-4	2-5	2-4.3
Tumor differentiation					
Well	1 (14.3%)	5 (41.6%)	4 (80%)	-	1 (25%)
Moderate	6 (85.7%)	7 (58.4%)	1 (20%)	2 (100%)	3 (75%)
Poor	-	-	-	-	-
No. of lymph nodes dissected	12 (Range: 10-32)	16.9 (Range: 5-26)	18.2 (Range: 13-20)	21.5 (12-30)	22.5 (16-32)
Lymph node involvement					
Involved	4 (57.14%)	6 (50%)	2 (40%)	1 (50%)	4 (100%)
Uninvolved	3 (42.86%)	6 (50%)	3 (60%)	1 (50%)	-
Lymphovascular invasion					
Present	5 (71.4%)	8 (66.7%)	3 (60%)	1 (50%)	4 (100%)
Absent	2 (28.6%)	4 (33.3%)	2 (40%)	1 (50%)	-
Perineural invasion					
Present	1 (14.3%)	5 (41.6%)	-	2 (100%)	4 (100%)
Absent	6 (85.7%)	7 (58.4%)	5 (100%)	0 (0%)	-
Resected margin status					
Involved	1 (14.3%)	-	-	1 (50%)	2 (50%)
Uninvolved	6 (85.7%)	12 (100%)	5 (100%)	1 (50%)	2 (50%)

**Table 4. Pathologic staging of malignant tumors.**

pT	n (%)
pT1	1 (3.23)
pT2	15 (48.39)
pT3	11 (35.48)
pT4	4 (12.9)

## DISCUSSION

Whipple pancreaticoduodenectomy is one of the most complex surgeries performed for the management of a variety of tumors involving the head of pancreas, ampulla of Vater, distal common bile duct or duodenum.<sup>12</sup> Although regarded as a life saving procedure, long term survival is largely dependent on the pathology within the resected specimen which emphasizes the need of meticulous evaluation of PD specimens.<sup>1</sup> We tried to report PD specimen with utmost care as per the protocol given by College of American Pathologists (CAP).<sup>13</sup>

In our study periampullary carcinoma was the predominant cancer on Whipple PD specimen which is in contrast to other studies. Duffy et al, Talamani et al

and Howe et al reported ampullary carcinoma as the predominant cancer.<sup>14-16</sup> We found ampullary carcinoma in only 5 cases (14.28%). This discrimination could be due to our strict adherence to the diagnostic criteria as proposed by Klimstra et al for the diagnosis of Ampullary carcinoma. According to them the tumor should be called as ampullary when the epicentre of the tumor is in the ampulla and there should be a pre invasive ampullary lesion. The tumor that grows circumferentially around the ampulla is called periampullary carcinoma.<sup>17</sup> Tumors predominantly in the periampullary duodenum with no significant involvement of ampulla are classified as periampullary duodenal where as those involving both periampullary duodenum as well as ampulla are described as periampullary mixed. Periampullary mixed tumor can either be exophytic or ulcerated.<sup>17</sup> We found eight of the periampullary mixed tumor presenting as exophytic mass (66.67%) whereas four of them were ulcerative (33.33%).

Western literature reveals pancreatic adenocarcinoma to be the commonest finding in PD specimens. In a review of 650 pancreaticoduodenectomies Yeo et al

found 43% cases to be pancreatic adenocarcinoma.<sup>1</sup> We found only four cases of pancreatic adenocarcinoma and one case of Pancreatic neuroendocrine tumor which is lower compared to their studies. This finding should however be interpreted with caution due to the small number of cases that we studied and an extensive study of larger sample size would highlight the true incidence of pancreatic malignancy in our country.

Histopathologically ampullary/ periampullary carcinoma can be of intestinal type, pancreaticobiliary type, mixed type and undifferentiated type. Categorization is important because the prognosis of the intestinal type is better than pancreaticobiliary type.<sup>17</sup> We found only one case of pancreaticobiliary carcinoma (4.1%) in contrast to studies done by Ibrahim et al and Howe et al who reported 6.7% and 27% respectively.<sup>16,18</sup> They reported most of the cases to be either well or moderately differentiated which is in agreement to our study.

Yeo et al performed a multivariate analysis of 443 patients with periampullary adenocarcinoma and reported four factors found to adversely affect survival: 1) tumor diameter  $\geq 3$  cm; 2) the presence of positive resection margins; 3) the finding of lymph node metastases in the resected specimen and 4) the presence of a poorly differentiated tumor. They also reported ampullary carcinomas to have the smallest tumor dimension with lower incidence of positive resection margins.<sup>1</sup> In our study we found the mean tumor diameter to be smallest in ampullary carcinoma (mean 2.2 cm). Moreover, 80% of these cases were well differentiated and resected margins were free of tumor in all cases. Positive resected margins were noted in two cases of pancreatic adenocarcinoma and one case each of periampullary duodenal and distal cholangiocarcinoma. Optimal histologic examination of a pancreaticoduodenectomy specimen should include analysis of a minimum of 12 lymph nodes.<sup>11</sup> The average number of lymph nodes recovered in our study was 12 which demonstrates adequate nodal dissection practised in our institute. In only three cases, five or less number of lymph nodes were harvested. When lymph nodes involvement by malignant tumor is taken into consideration (including one neuroendocrine tumor), 17 cases (54.8%) showed lymph node metastasis which is significantly higher as compared to studies done by Ibrahim et al (10%) and Allema JH et al (40%).<sup>18,19</sup> Furthermore fifteen cases were diagnosed to be in advanced stages (T3 or higher). This shows many of our patients are diagnosed in advanced stages with widespread lymph node metastasis. Hence precise assessment of signs and symptoms along with correlation with radiological/ other laboratory findings should be emphasized for early diagnosis of cancer.

In the large series of 1175 resected pancreatic cancers by Winter et al., the incidence of perineural invasion was 91% whereas vascular involvement was lower (53%).<sup>20</sup> In our study, patients with pancreatic cancer had the highest incidence of lymphovascular invasion (100%) and perineural invasion (100%) which have been shown to be poor prognostic features. Pancreatic cancers also had a 50% incidence of microscopic margin involvement which was higher than that of ampullary, periampullary duodenal and periampullary mixed carcinoma. Chandrasegaram et al have reported clear margin in 46% of patients prior to 2010 and 67% of patients after 2010. They have concluded this change might be due to the improvement in their surgical technique.<sup>5</sup> Margin status has been shown to relate to survival outcomes. Yeo et al. showed in their series of 201 patients that the five year survival in those with a negative margin was 26% (median survival 18 months) compared to those with a positive margin 8% (median survival 10 months).<sup>21</sup> Whilst margin positivity appears to be critically important, not all margins may have a similar impact on patient survival. Delperio et al. reported that a positive Superior Mesenteric Artery (SMA) or Superior Mesenteric Vein (SMV) margin had a significant impact on progression-free survival, a positive posterior margin had no impact.<sup>22</sup> In our study both of the pancreatic cancers had SMA margin involvement.

Two of the cases suspected of malignancy in our study turned out to be benign on histopathology. One of the cases suspected of Periampullary carcinoma was found to be periampullary adenomatous hyperplasia while another case thought to be a distal cholangiocarcinoma showed only non-specific inflammation. The diagnostic work-up for patients with presumed cancer is complex, costly and not always accurate. Studies have shown the incidence of benign histopathology on PD specimens could be as high as 13%.<sup>23</sup> In a report from Mayo Clinic, Smith et al. reviewed 484 patients who underwent Whipple procedure for suspected periampullary malignancy and found chronic inflammatory disease on final pathologic assessment in 24 patients (5%).<sup>24</sup> vanGulik et al. described 220 patients who underwent Whipple and reported 6% benign findings. They suggested that at least 5% of benign finding is expected when performing PD for a suspected malignant disease. Given the grim prognosis of the pancreatic cancer this should not stop surgeons from performing the procedure on patients with clinically suspected malignancy but with no other confirming data.<sup>25</sup> Number of carcinoma mimics including adenomyoma of the ampulla, papillary hyperplasia, sclerosing papillitis, benign biliary and duodenal disease have been identified. Adenomatous hyperplasia of the ampulla is larger than 0.5 cm and contains complex glands, arranged in a lobular

architecture surrounded by the lamina propria and muscle bundles. Its presentation in the elderly individual and its obstructive symptoms may point towards malignancy, but it is distinguished by its architecture and lack of dysplasia and mitosis.<sup>26-28</sup> Two cases in which the final histopathologic diagnosis of serous cystadenoma and noninvasive mucinous cystic neoplasm with low grade dysplasia were made, preoperative radiological diagnosis suggested mucinous cystadenoma. Interestingly, in two cases of periampullary carcinoma, concomitant tubercular lymphadenitis was observed which highlights the impact of Tuberculosis in our community.

## CONCLUSIONS

Pancreaticoduodenectomy specimen requires meticulous histopathologic evaluation for proper categorization of histologic type and other features which affect patient survival following PD. Possibility of a benign diagnosis remains in PD specimen which have been resected presuming malignancy based on clinical judgement and radiological data.

**Conflict of Interest: None.**

## REFERENCES

1. Yeo CJ, Cameron JL, Sohn TA, Lillemoe KD, Pitt HA, Talamini MA et al. Six Hundred Fifty consecutive Pancreaticoduodenectomies in the 1990s. *Ann Surg* 1997; 226:248-57.
2. Whipple AO, Parsons WB, Mullins CR. Treatment of carcinoma of the ampulla of Vater. *Ann Surg* 1935; 102:763-79.
3. Birkmeyer JD, Finlayson EVA, Siewers AS et al. Hospital volume and surgical mortality in the United States. *N Engl J Med* 2002; 346: 1137-44.
4. Kennedy EP, Rosato EL, Sauter PK et al. Initiation of a critical pathway for pancreaticoduodenectomy at an academic institution – the first step in multidisciplinary team building. *J Am CollSurg* 2007; 204:917-23.
5. Chandrasegaram MD, Chiam SC, Chen JW, Khalid A, Mittinty ML, Neo EL et al. Distribution and pathological features of pancreatic, ampullary, biliary and duodenal cancers resected with pancreaticoduodenectomy. *World Journal of Surgical Oncology* 2015; 13:1-7.
6. He J, Ahuja N, Makary MA, Cameron JL, Eckhauser FE, Choti MA, et al. 2564resected periampullary adenocarcinomas at a single institution: trends overthree decades. *HPB*. 2014;16:83–90.
7. Chen JWC, Bhandari M, Astill DS, Wilson TG, Kow L, Brooke-Smith M, et al. Predicting patient survival after pancreaticoduodenectomy for malignancy: histopathological criteria based on perineural infiltration and lymphovascular invasion. *HPB*. 2010;12:101-8.
8. Martin FM, Rossi RL, Dorrucchi V, Silverman ML, Braasch JW. Clinical and pathologic correlations in patients with periampullary tumors. *Arch Surg* 1990;125:723-26.
9. Bouvet M, Gamagami RA, Gilpin EA, Romeo O, Sasson A, Easter DW, et al. Factors influencing survival after resection for periampullary neoplasms. *Am J Surg* 2000; 180:13-17.
10. Badger SA, Brant JL, Jones C, McClements J, Loughrey MB, Taylor MA, et al. The role of surgery for pancreatic cancer: a 12-year review of patient outcome. *Ulster Med J* 2010;79:70-75.
11. Stephen Edge, Byrd DR, Compton CC, Fritz AG. *AJCC Cancer staging manual*. Seventh Edn. Chicago: Springer; 2010. Chapter 23, Ampulla of vater; 277-281.
12. Forough F, Mohsenifar Z, Ahmadvand A, Zare K. Pathologic findings of Whipple pancreaticoduodenectomy: a 5-year review of 51 cases at Taleghani general hospital. *GastroenterolHepatol Bed Bench* 2012;5(5):179-82.
13. Protocol for the examination of specimens from patients with carcinoma of the ampulla of Vater. Based on AJCC/ UICC TNM, 7<sup>th</sup> edition.
14. Duffy JP, Hines OJ, Liu JH, Ko CY, Cortina G, Isacoff WH et al. Improved survival for adenocarcinoma of the ampulla of vater: fifty five consecutive resections. *Arch Surg*. 2003; 138:941-50.
15. Talamini MA, Moesinger RC, Pitt HA, Sohn TA, Hruban RH, Lillemoe KD et al. Adenocarcinoma of the ampulla of vater. A 28-year experience. *Ann Surg*. 1997;225:590-600.
16. Howe JR, Klimstra DS, Moccia RD, Conlon KC, Brennan MF. Factors predictive of survival in ampullary carcinoma. *Ann Surg*. 1998;228(1):87-94.
17. Mills S, Carter D, Greenson J, Reuter V, Stoler M. *Diagnostic Surgical pathology*. Fifth Edn. Wolters Kluwer, Lippincott Williams & Wilkins; 2010. Chapter 38, Gallbladder, Extrahepatic biliary tract and Ampulla; 1636-1637.
18. Ibrahim SS, Kumari M. Analysis of Whipple resection specimens: A Histopathological Perspective. *Annals of Pathology and Laboratory Medicine* 2016;3(2):105-13.
19. Allema JH, Reinders ME, van Gulik TM, et al. Results of Pancreaticoduodenectomy for ampullary carcinoma and analysis of prognostic factors for survival. *Surgery* 1995; 117:247-53.
20. Winter JM, Cameron JL, Campbell KA, Arnold MA, Chang DC, Coleman J, et al. 1423 Pancreaticoduodenectomies for pancreatic cancer: a single institution experience. *J Gastrointest Surg*. 2006;10:1199-211.
21. Yeo CJ, Cameron JL, Lillemoe KD, Sitzman JV, Hruban RH, Goodman SN et al. Pancreaticoduodenectomy for cancer of the head of the pancreas. 201 patients. *Ann Surg*. 1995;221:721-33.

23. Delpero JR, Bachellier P, Regenet N, Le Treut YP, Paye F, Carrere N, et al. Pancreaticoduodenectomy for pancreatic ductal adenocarcinoma: a French multicentre prospective evaluation of resection margins in 150 evaluable specimens. *HPB*.2014;16:20-33.
24. Barone JE: Pancreaticoduodenectomy for presumed pancreatic cancer. *SurgOncol* 2008; 17:139-44.
25. Smith CD, Behrns KE, van Heerden JA, Sarr M. Radical pancreaticoduodenectomy for misdiagnosed pancreatic mass. *The British Journal of Surgery* 1994;81(4):585-89.
26. vanGulik TM, Reeders JWAJ, Bosma A et al., Incidence and clinical findings of benign, inflammatory disease in patients resected for presumed pancreatic head cancer. *Gastrointestinal Endoscopy* 2003; 43(5):417-23.
27. Al Jitawi SA, Hiarat AM, Al-Majali SH. Diffuse myoepithelialhamartoma of the duodenum associated with adenocarcinoma. *ClinOncol* 1984;10:289-93.
28. Bergdahl L, Anderson A. Benign tumors of the papilla of Vater. *Am Surg* 1980; 46:563-6.
29. Wojcicki J, Zen Y, Peddu P, Jain R, Patel AG, Atkinson S et al. Benign histology after pancreaticoduodenectomy for suspected malignancy. Lessons to be learned – A single centre experience. *PolskiPrzeglądChirurgiczny* 2015;87(1):6-15.