

RESEARCH COMMUNICATION

Morphology, TNM Staging and Survival with Pancreatico-duodenectomy Specimens received at Shaukat Khanum Memorial Cancer Hospital and Research Centre, Pakistan

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Abstract

Background: Whipple specimens consists of duodenum from the pylorus to the ligament of Treitz, the head of the pancreas and distal extrahepatic biliary tract, sometimes with most distal portion of the stomach. Adequate gross handling of the specimen and assessment of histological variables is of prognostic importance. **Methods:** At the Pathology Department of Shaukat Khanum Memorial Cancer Hospital and Research Centre, we here evaluated survival with a total of 65 pancreaticoduodenectomy specimens from 2006 to 2010 with reference to histological parameters like tumour type, site, size, grade, pT, pN, margin status and perineural invasion, and compared our results with international data. Patients were followed up and P-values were calculated regarding association between survival and prognostic factors, Kaplan-meier survival curves also being plotted. **Results:** Most of the patients were males (60%), with a mean age of 50 yrs. The most frequent site was periampullary region (43.2%), with adenocarcinoma, NOS accounting for 72.4%. G2 was the most common grade (58.5%) and the most frequent pT was pT2 (52.4%), nearly half presenting with lymph node metastasis (47.7%). Significant associations ($p < 0.05$) were noted for survival with grade, pT, pN, margins, tumor size and perineural invasion, but not tumor site, tumor type and age. Kaplan-Meier curve revealed that at end of 1 month, 70% of the patients were alive, this decreasing to 40%, 15% and 5% and at the end of 6 months, 1 year and 2 years. **Conclusion:** Tumor size, type, pathologic T and N staging, margins and perineural invasion are directly related to survival with pancreatico-duodenal lesions.

Keywords: Pancreatico-duodenectomy specimens - prognostic factors - survival - Pakistan

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Introduction

The Whipple procedure was first performed by Kausch in 1908, later on being popularized by Whipple in the 1930s. A modified technique called pylorus preserving pancreatico-duodenectomy (Beger et al., 2008) is associated with lesser complications. This surgical approach is indicated for carcinomas of the pancreatic head, cholangiocarcinomas, ampullary and periampullary tumors, primary duodenal tumors and pancreatitis producing mass effects. Pancreatic adenocarcinomas of the body or tail usually present late (because they don't obstruct) with extension into peripancreatic tissue and metastasis and rarely resectable (Mu et al., 2004). Resectable tumors of the region are more likely to be tumors of the ampullary region (presenting with obstruction), endocrine tumors or unusual non-endocrine tumors (cystic lesions such as cystadenoma or cystadenocarcinoma). Benign conditions for example pancreatic pseudocyst or chronic pancreatitis are resected less frequently (Thomas et al., 2010). On initial examination of the fresh specimen, the following anatomic

structures should be identified: common bile duct margin, pancreatic tissue margin, stomach or duodenum and the distal duodenal margin. Peripancreatic soft tissue margins should be inked before processing (Kayahara et al., 2010). At least two enface sections of the pancreatic resection margin including the pancreatic duct should be performed at the outset to assess the pancreatic margin.

According to the guidelines of college of American pathologists, there are many parameters of prognostic importance, including histological tumor type, tumor size, site, grade, stage (pT), lymph node status (pN), margin status, perineural and lymphovascular invasion (Lazaryan et al., 2008). Due to improved surgical skill and peri-operative care, operative mortality rates which was 20%-40% in earlier days have dramatically decreased with the Whipple procedure and currently are between 0- 4% in experienced centers, although complication rates are still 30%-40%. In one series the overall 5-year survival for stage I tumors was 84%, stage II 70% and stage III 27% (Morris-Stiff et al., 2009). The present study was conducted to generate data for use of this surgical approach in Pakistan.

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Materials and Methods

This study was carried out at Pathology Department of Shaukat Khanum Memorial Cancer Hospital And Research Centre from 2006 to 2010, over a period of five years. All Pancreaticoduodenectomy procedures done for malignancies were included. These specimens included specimens of hospital registered patients as well as surgeries performed outside the hospital and specimens sent to histopathology section for gross and histologic evaluation. Mean, median and mode were calculated for quantitative variables like patient, tumor size and survival in months. Frequencies and percentages were calculated for qualitative variables like tumor type, site, grade, pathological stage (pT), lymph node status (pN), margin status, perineural invasion and age. All ages and both genders were included. Morphological and histological parameters were recorded according to the guidelines of college of American pathologist. All the patients were contacted through their phone numbers. Patients were divided into five survival groups; < 1 month, 1 – 6 months, >6 – 12 months, >12-24 months, alive patients. P values were calculated regarding association of survival with pathological stage (pT), grade, lymph node status (pN), tumor size, and margin status and perineural invasion. Kaplan-Meier curve was also plotted for the dead patients.

Results

Mean age was 50.2+12.9 years. Most frequent age group was 5th (29.3%) and 6th (21.6%) decade. Fourth and seventh decades comprised 20% of the patients each. Out of total of 65 patients, 39 (60%) were males and 26 (40%) were females. A total of 7 (10.7%) patients remained alive for less than 1 month, 10 (16.9%) for 1 to 6 months, 6 (9.2%) greater than 6 to 12 months and 4 (6.1%) for greater than 12 to 24 months. About 27 (41.5%) patients are still alive, whereas we were unable to contact 11 (15.6%) patients.

Mean tumor size was 2.5+1.5 cm with tumor size range of 0.6 cm to 7.5 cm. About 57% of the tumors were less than or equal to 2.5 cm, 34% greater than 2.5 cm but less than 5 cm. Rest (9%) were more than 5cm. Most frequent sites in descending order of frequency were periampullary region (43.2%), ampulla (30.7%) and pancreas (26.1%). Commonest tumor was adenocarcinoma, NOS (72.4%) and ductal adenocarcinoma (13.9%). Other tumors included neuroendocrine tumor, papillary adenocarcinoma, adenocarcinoma intestinal type and adenosquamous carcinoma. Regarding pathological stage, pT2 was most common 34 (52.4%), followed by pT3 19 (29.2%), pT1 (10.8%) and pT4 5 (7.6%). About 38 (58.5%) of tumors were grade2, 18 (27.6%) grade1 and 9 (13.9%) grade 3. A total of 31 (47.7%) of the patients had lymph node metastasis. Most of the patients with lymph node metastasis (pN1) had grade2 (58%) and grade 3 (22.6%) tumors, belonged to pT2 (35.4%) and pT3 (45.2%) stage and had tumor size more than 2.5cm (51.7%). Retroperitoneal margin was involved in 13.8% of cases and pancreatic margin in 4.6% of the cases. Perineural invasion was seen in 12.4% of the cases.

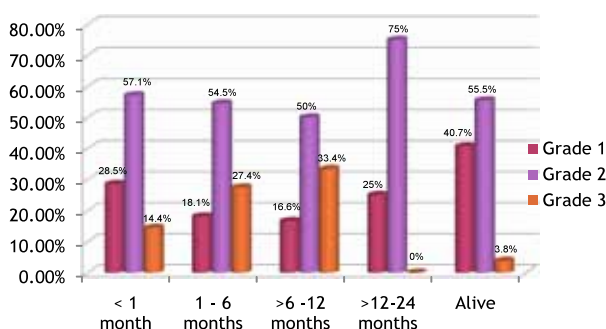


Figure 1. Relationship of Survival with Histological Grade

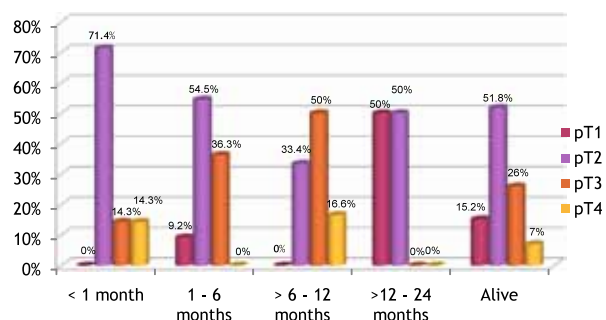


Figure 2. Relationship of Survival with pT

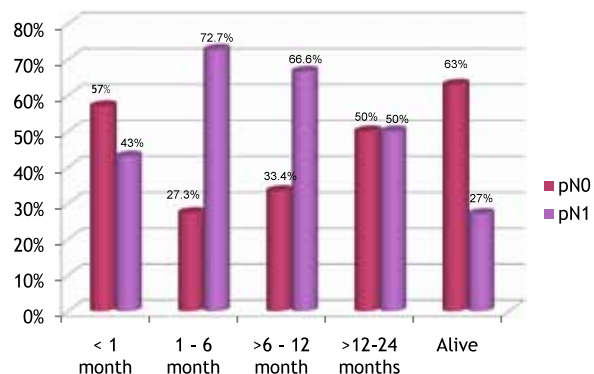


Figure 3. Relationship of Survival with Lymph Node Status

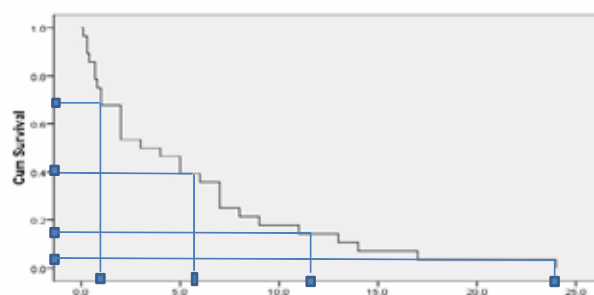


Figure 4. Kaplan-Meier Survival Analysis (in months)

As the survival increased in months, percentages of the patients with grade 1 and grade 2 tumors increased and that of grade 3 tumors decreased, with only 3.9% of grade 3 tumors in alive patients ($p < 0.05$) (Figure 1). For pathological staging, as the survival increased in months, frequencies of patients with pT1 and pT2 increased and pT3 and pT4 decreased to very low percentages in patients surviving for more than 12 months ($p < 0.05$) (Figure 2). Likewise, for lymph node status, as the survival

increased, patients with lymph node metastasis decreased in frequency ($p < 0.05$) (Figure 3). Similar were the results for tumor size. About 75% of the patients with tumor size less than 2.5 cm survived for more than 12 months and also 63% of the alive patients had tumor size less than 2.5 cm ($p < 0.05$). About 97% of the patients with uninvolved pancreatic margin and 82% of the patients with uninvolved retroperitoneal margins are still alive ($p < 0.05$). Our study revealed significant association of survival with tumor grade ($p < 0.002$), lymph node status ($p < 0.002$), pT ($p < 0.004$), margin status ($p < 0.001$), tumor size ($p < 0.001$) and perineural invasion ($p < 0.001$). However we did not find any association of tumor type, age and tumor site with survival ($p > 0.05$).

When Kaplan-Meier curve was plotted for dead patients, it was found that at the end of 1 month, 70% of the patients were alive, and at the end of 6 months 40% of the patients were alive, whereas at the end of 12 months only 15% were alive (Figure 4).

Discussion

Prognostic pathologic features when signing out carcinoma of pancreas and ampulla are considered separately. Even the checklist and TNM classifications for either of these tumors are different. T1 tumor is limited to pancreas and is 2.0 cm less in greatest dimension. T2 tumor is limited to pancreas more than 2.0 cm in greatest dimension and T3 tumor extends beyond the pancreas but without involvement celiac axis or superior mesenteric artery. Involvement of celiac axis or superior mesenteric upstages the tumor to pT4. Going on to the TNM for tumors of ampulla of vater, T1 is tumor limited to ampulla of vater or sphincter of oddi. T2 tumor invades duodenal wall. T3 tumor invades into pancreas. T4 is tumor invades peripancreatic soft tissue or into the adjacent organs or structures. There are many histological features of prognostic importance. Multifocal tumors have grave prognosis as compared to unifocal tumours. Tumor size is an important criterion because TNM classification is based on tumor size. Histological tumor type, histological grade, perineural invasion, margin status and lymph node status bear prognostic significance (Lazaryan et al., 2008). For duodenum and ampulla, tumor site whether intra-ampullary, peri-ampullary or at junction of Ampulla and duodenal mucosa is important (Beger et al., 2008). Tumors with size less than 2.5 cm in greatest dimension have 65% 5 years survival whereas tumors more than 2.5 cm have 25% 5 year survival rates. Histological tumor type, tumor grade, extent of invasion whether tumor is in situ or invasive into adjacent organ, presence of intraductal lesions, lymphovascular invasion, margin status and nodal status are important indicators of prognosis (Thomas et al., 2010).

We compared our study with various old and new studies (Chareton et al., 1996; De Castro et al., 2004; Beger et al., 2008) regarding two year survival. In all above mentioned studies 2 year survival decreased as the value of pT increased from pT1 to pT4. It was at least 50% for patients with pT1 stage and less than 20% for patients with advanced pT4 stage in nearly all aforementioned studies.

The patients without lymph node metastasis were almost 50% in all studies, whereas it was about 26% in study by Bottger et al (1999). In our study number of patients with lymph node metastasis had increasing trend as the pT value increased, being highest for pT3 and pT4 patients. Results were similar to earlier studies (Yamaguchi et al., 1991; Allema et al., 1995; Bottger et al., 1999; De Castro et al., 2004; Beger et al., 2008; Kayahara et al., 2010) Our study had lower percentage of lymph node metastasis for pT4 patients, possibly due to the low number. Our study revealed significant association of survival with tumor grade, lymph node status, pT, margin status ($p = 0.001$), tumor size and perineural invasion. In earlier studies (Mu et al., 2004; Lazaryon et al., 2008; Morris-Stiff et al., 2009; Thomas et al., 2010), the association of survival with lymph node metastasis was significant ($p < 0.05$). Survival was found associated with pT and margin status (Lazaryon et al., 2008; Morris-Stiff et al., 2009). Tumor size was also associated with survival in some (Mu et al., 2004; Thomas et al., 2010), but not other studies (Lazaryon et al., 2008). Similar variation was revealed with perineural invasion (Mu et al., 2004; Thomas et al., 2010).

Survival had no correlation with histological tumor type, age of the patient and tumor site in our study. Also Mu et al (2004) and Thomas et al (2010) did not find any effect of histological tumor type on survival. Only the latter found an association of survival with site. In all of the above mentioned studies, patients survival decreased markedly with each passing year, as in our cases.

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