Journal of Medical and Surgical Practice (JMSP)
Vol. 08, No. 01, January-March, 2022

Comparison of Two Palliative Approaches in patients with Pancreatic Head Adenocarcinoma- Clinical Evaluation and Outcome

Dr. Hayder Radhi Abdulshaheed[1], Dr. Wisam Saud Ahmed[2]

Dr. Ali Hashim Abbood[3]

1. MBChB, F.I.C.M.S , F.A.C.S, Najaf GIT center

2. MBChB, F.I.C.M.S, C.A.B.S, Surgeon, Mosul GIT centerMBChB, C.A.B.S , F.I.C.M.S, Najaf GIT center

3. MBChB, C.A.B.S , F.I.C.M.S, Najaf GIT center

**Corresponding Author*

Original Article

Abstract

***Background**: Surgical bypass and endoscopic endoprosthesis are the common two palliation methods in patients with pancreatic head adenocarcinoma. No strong evidence about which method can be proffered, the question still to be answered.*

***Objective**: To compare the outcomes of Surgical bypass and endoscopic stenting as palliative treatment for Iraqi patients with locally advanced pancreatic adenocarcinomas*

***Patients and Methods**: This was a comparative study conducted during a period of three years, included 74 Iraqi patients of both genders with unresectable pancreatic head adenocarcinomas and equally assigned into two groups to have palliative treatment with either surgical bypass (group 1) or endoscopic stenting (group 2). Patients selected from two centers; Mosul and Najaf GIT centers. All patients were followed up for a median duration of 15 months.*

***Results:** Both studied groups were almost matched for age and gender. No significant differences were reported in early complications; sepsis and bleeding between the studied groups, (P>0.05). in endoscopic stenting group 4 patients (10.8%) had stent blockage or bypass. Two patients (5.4%) in palliative surgery group and 6 patients (16.2%) in the endoscopic stenting group died within thirty days, (P>0.05). Late complications and mortalities were more frequent in endoscopic stenting group. The overall survival in patients of palliative bypass surgery was significantly better than that in the endoscopic stenting group with a median survival of 386 days vs. 139 days, respectively, (P<0.05).*

***Conclusion**: Surgical bypass palliation offers lower rate of late complications, readmission and lower mortality rates and was associated with higher overall survival rate.*

***Keywords:** Pancreatic adenocarcinoma, Palliative surgical bypass, endoscopic stenting, Complications, Survival rate*

***Article information**: Received: January,2022 , Published online: March,2022*

***How to cite this article**:*
Abdulshaheed H.R, Ahmed W.S, Abbood A.H, Comparison of Two Palliative Approaches in patients with Pancreatic Head Adenocarcinoma- Clinical Evaluation and Outcome, JMSP 2022, 8(1): 291-309

1. INTRODUCTION

Pancreatic cancer is a disease that even today, has a dismal prognosis. It ranks fourth as a cause of death in the United States in men and fifth in women. There are many reasons why these patients, when diagnosed, suffer from an incurable disease, vascular invasion and metastasis are the main causes of poor prognosis. Pancreatic adenocarcinoma is the most common malignancy of the pancreas contribute for almost 85% of pancreatic malignancies and majority of these adenocarcinomas located at the head of pancreas. Pancreatic adenocarcinoma had very poor prognosis because vast majority of patients presented at advanced stages, so they are not candidate for resection (1). It is one of the most fatal cancers all over the world, the relative 5-year survival is about 8.5%-9% in 2018 (2,3) the survival rate affected by age of patients at diagnosis, stage of cancer, degree of differentiation and surgical resection. Usually, pancreatic adenocarcinomas present with the presence of liver metastasis or peritoneal carcinomatosis which worsen the prognosis (4).

Globally, pancreatic cancers rank the 12th among all malignancies and represent the 7th leading cause of mortality of all cancers' deaths. To date, no sufficient evidence about the causes of pancreatic cancer, however, some risk modifiable and non-modifiable factors have been identified, like age, gender, ethnicity, genetic factors, family history, chronic pancreatitis, exposure to certain chemicals, obesity, smoking, alcohol abuse, diabetes mellitus, dietary factors, infection with Helicobacter pylori and non-O blood group (3,5).

In Iraq, most of the risk factors are commonly prevalent and the incidence rate of pancreatic cancer among Iraqi population has continue to increase in the last decade, it was 0.71/100,000 in 2000, 0.76/100,000 in 2008 and reached 1.446 in 2016 according to the last updated data (6,7).

As the pancreatic cancer almost diagnosed at advanced stages, no screening program is considered useful in general population for large groups, nonetheless, new techniques are being evaluated in certain groups particularly those with family history (3).

Pancreatic cancer is usually asymptomatic in the early stages, the symptoms and signs appear late, since a high percentage of patients present with locoregional invasion. Abdominal pain is the most frequent symptom, most of patients present marked jaundice, which occurs due to obstruction of the intrapancreatic portion of the bile duct, due to infiltration of the pancreatic

head tumor. Jaundice begins insidiously but is invariably progressive. Sometimes, pancreatic cancer presents with nonspecific symptoms; constitutional syndrome (striking weight loss, asthenia, and anorexia) and cachexia, diarrhea with steatorrhea, diabetes mellitus, nausea, vomiting, migratory thrombophlebitis, and gastrointestinal bleeding or as acute pancreatitis. Physical examination may reveal jaundice, scratching lesions, palpation of a distended gallbladder, hepatomegaly. In advanced stages, palpable liver metastases, lymphadenopathy and ascites due to peritoneal carcinomatosis, or less frequently due to portal hypertension.(11).

Over the past two decades, numerous advances have been made in preoperative staging, aiming to improve survival rate of patients early detection and prove diagnosis. Computed tomography (CT), helical abdominal tomography, magnetic resonance imaging (MRI), magnetic resonance cholangiography (MRCP) and endoscopic ultrasound, as well as retrograde endoscopic approach to laparoscopic surgery, have allowed minimally invasive methods to determine the resectability of the tumor, obviating the need for surgical exploration. Despite the role of these techniques in better detection of tumors by enhancement of thorough analysis of morphological parenchymal changes of pancreas and pancreatic ducts, the diagnosis could be improved by positron emission tomography. However, the diagnosis rely mainly on the surgeons and clinicians decisions to understand the advantages and disadvantages of different modalities in order to choose the optimal treatment and management options (8–11).

Unfortunately, majority of patients with pancreatic cancer are present with unresectable disease, and even with successful resection and with tumor-free margins the 5-year survival rate still within 10%-25% , and local tumor recurrence is common after surgical resection and is one of the determining factors of survival (12). However, a majority of patients are not candidates for surgical resection for curative purposes. but probably the only possibility to obtain a better quality of life. The palliation that occupies a decisive role in the treatment of this disease Currently, the real debate focuses on what is the best palliative method to use and not to whom it should be applied. Systemic chemotherapy, radiotherapy and some other management options like minimally invasive image-guided procedures are mainly use in management of patients with adenocarcinoma of pancreas when they are non-operable

(12,13).

Palliative treatment is usually performed to relieve the jaundice. Biliary-enteric surgical bypass has been the treatment of choice for palliation of obstructive jaundice for many years. However, laparoscopic procedures has been introduces as a successful alternative for open surgery, on the other hand metallic stenting has been also reported to be minimally invasive, safe and effective procedure (14). The selection of surgical procedures; surgery or endoscopic drainage still subjective and rely on the preferences of the surgeons, availability of technique and patient status. Among GIT surgeon, palliative management to ascertain biliary drainage, has been of great interest. However, some studies have shown no difference in the efficacy of endoscopic drainage and surgical treatment (14–16). Therefore, there are various therapeutic options been described; palliative resection, is one of the commonest options that it may provide a better or improved survival and have morbidity and mortality rates equivalent to surgical bypass surgery (12–14). Other options are also investigated for palliation in unresectable pancreatic cancer such as Choledochoduodenostomy (17), Palliative laparoscopic Roux-en-Y choledocho-jejunostomy as a feasible treatment option (18) and biliary endoprostheses based on using titanium alloys and 3D printing techniques (19).

The endoscopical stenting provide the ability to use larger caliber endoprosthesis, as a minimal invasive technique well tolerable by the patients, which considered as an advantage of this palliation method, nonetheless, some limitations are accompanied its use that may render repeated stenting is inapplicable or impossible, the recurrence of jaundice due to stent migration, progression of tumor and invasion of duodenum are the main limitations of palliative potential (20,21).

Therefore we aimed to compare the outcomes of Surgical bypass and endoscopic stenting as palliative treatment for Iraqi patients with locally advanced pancreatic adenocarcinomas.

2. PATIENTS and METHODS

This was a comparative study conducted during a period of three years; a mixed design was used in this study where a prospective and a retrospective design were utilized. Retrospective data were collected during the years 2018, 2019, with a total of 53 cases, the data collection

was hold during the COVID-19 pandemic, then resumed in 2021, where a total of 21 cases prospectively included using consecutive sampling technique. The data collected from Najaf GIT center, Mosul GIT center and private clinics of the authors. The total patients included in the study were 74 patients from both centers.

Inclusion criteria:

1. Iraqi patients of with primary locally advanced adenocarcinoma of head of pancreas.
2. Planned for palliative treatment due to their malignant obstructive jaundice
3. Age 40 years or older
4. Of both genders.

Exclusion criteria:

Patient with one or more of the following was excluded from the study

1. Proved histopathological diagnosis of non-adenocarcinomas.
2. Metastasis.
3. Ascites (proved by imaging and clinical examination).
4. Normal tumor marker, CA19.9 (lower than 37 IU/L)

Study protocol:

1. Patients were assigned into two equal groups (36 patients in each) and were compared. First group included those who treated with Stenting and/or chemotherapy. The second group included those who underwent palliative surgery and/or chemotherapy. However, the assignment of patients to either group relied on the preferences of the patient and decision of surgeon regarding the fitness of patient for operation.
2. The date of first CT scan was depended as date of diagnosis
3. Size of Tumor and stage based on surgical and imaging reports.
4. Definite diagnosis when no histopathology report available, based on clinical data, imaging reports such as ultrasound, CT scan or MRI in addition to tumor markers. According to reference values of national laboratories in Iraq, CA19.9 of more than 37 IU/L was considered significant.

Treatment Techniques:

Endoscopic stenting procedure

In stenting group, we used self-expanding metallic stent with a length of 5 cm and a width of 8 mm. Started with side-viewing duodenoscope the stent was placed under fluoroscope guide. Stent placement was confirmed by anatomic position, observation of bile drainage, and post-stenting administration of contrast medium to confirm position above the bile duct.

Surgical bypass technique

In the second group of palliative surgical bypass, all patients were managed under general anesthesia. A triple bypass was performed included hepato-jejunostomy Roux-en-Y and side to side anastomosis and gastro- jejunostomy

Outcome and follow up:

Outcome of patients was started postoperatively, looking for early postoperative complications. During the follow up period, short and long term complications, morbidity, hospital readmission were observed and reported. Perioperative complications (occurring within 30 days after stent placement or surgery) were carefully monitored and been reported. Additionally, any mortality within 30 days was documented with clarification of the cause of death. Survival rates reported according to the follow up and hospital records. Patients were followed up from two weeks to 21 months with a median of 15 months of follow up

Data collection, management and analysis:

Data of the patients were collected using a pre-constructed data collection sheet, including three sections, the first for demographic characteristics of the patients; age, gender, residence, family history, occupation, medical history, surgical history, duration of disease, …., etc. The second section for the clinical , laboratory and imaging findings and the third section for operative findings and follow up (complications, readmission , morbidities mortalities and survival).

Data were entered, managed and analyzed using the statistical package for social sciences version 26, Microsoft Office Excel program version 2019 and Epi-calc-2000 software. Statistical tests and procedures were applied according to the type of variables. Descriptive statistics presented as mean, standard deviation (SD), median, frequencies and proportions. Student's t test used to compare means for a continuous variable in between two groups, Chi-

square test and Fisher's exact test used to compare categorical variables. Survival was analyzed using log-rank and Kaplan-Meier analyses. All statistical tests and procedures applied under the assumption of two tailed alpha level (P. value) of 0.05 or less to be statistically significant at a level of confidence of 95%.

3. RESULTS

In this study, 74 patients were recruited, represented the both treatment groups with 37 patients in each, both groups were almost matched for age and gender with no statistically significant difference in age group, mean age and gender, in all comparisons, P. value > 0.05, however, more than 65% of patients in both groups, aged 60 years or older. On the other hand, males were relatively dominant compared to females; males represented 56.8% and 51.4% in Palliative surgery and Endoscopic stenting groups, respectively (Table 1).

No significant difference was found between the studied groups in mean tumor size, (P>0.05), (Figure 1), a significant lower mean CA-19.9 value in bypass group, (P<0.05), (Figure 2) and no significant difference in mean total serum bilirubin (TSB), (P>0.05), (Figure 3).

Early complications reported after intervention were not significantly different between groups, (P. value >0.05), however, sepsis reported in 43.2% of patients in palliative surgery group compared to 21.6% in endoscopic stenting group. Bleeding reported in 13.5% and 18.9%, respectively. Additionally, in endoscopic stenting group 4 patients (10.8%) had stent blockage or bypass. Regarding the mortality within thirty days, 2 patients (5.4%) in palliative surgery group and 6 patients (16.2%) in the endoscopic stenting group died within thirty days after intervention, however, the difference in mortalities was statistically insignificant, (P>0.05), (Table 2). It is worth mentioned that causes of death were respiratory infection complicated by multiple organ failure, other respiratory complications acute cholangitis, acute renal failure, upper GIT bleeding, and, Regarding the late complications, cholangitis reported in 3 patients of palliative surgery and two patients of endoscopic stenting group, abdominal pain in 4 patients in each group, both complications were not significantly different between both groups, (P. value > 0.05).

Recurrent jaundice reported in only 10 patients of endoscopic stenting group and it was significantly different than palliative surgery group where no recurrent jaundice reported, (P. value =0.002, significant). Readmission was significantly less frequently needed in palliative

surgery group compared to endoscopic stenting group in a rate of 13.5% vs. 45.9%, respectively, (P. value = 0.005, significant). After excluding the admission due to chemotherapy related problems, the duration of hospital stay in surgical bypass group was significantly shorter than that in the endoscopic stenting group (11.1 days) compared to (35.4 days, respectively. Obstruction of bypass, sepsis and Gastric outlet obstruction (G.O.O), were the main reasons of readmission.

Late mortality after 30 days was zero in palliative surgery group and 8.1% in endoscopic stenting group, despite this lower mortalities in palliative surgery group, but the difference was statistically insignificant, (P. value>0.05), (Table 3 and Figure 4).

The overall survival in patients of palliative bypass surgery was significantly better than that in the endoscopic stenting group with a median survival of 386 days compared to 139 days, respectively, (Figure 5). Further analysis was performed to assess the effect of preoperative CA 19.9 on the survival rate which appeared to significantly influence the survival where patients who had preoperative CA 19.9 value of less than 1000 IU/L in both groups were significantly survived longer than those with CA 19.9 of more than 1000 IU/L, (Figure 6).

Table 1. Age and gender distribution of the studied groups

Variable		Palliative Surgery (n=37)		Endoscopic stenting (n=37)		P. value
		No.	%	No.	%	
Age (year)	40 - 49	3	8.1	4	10.8	0.855 ns
	50 - 59	10	27.0	7	18.9	
	60 - 69	18	48.6	19	51.4	
	≥ 70	6	16.2	7	18.9	
	Mean (SD)	58.2 (8.1)	-	57.6 (9.3)	-	0.768 ns
Gender	Male	21	56.8	19	51.4	0.816 ns
	Female	16	43.2	18	48.6	

ns: not significant, SD: standard deviation of mean

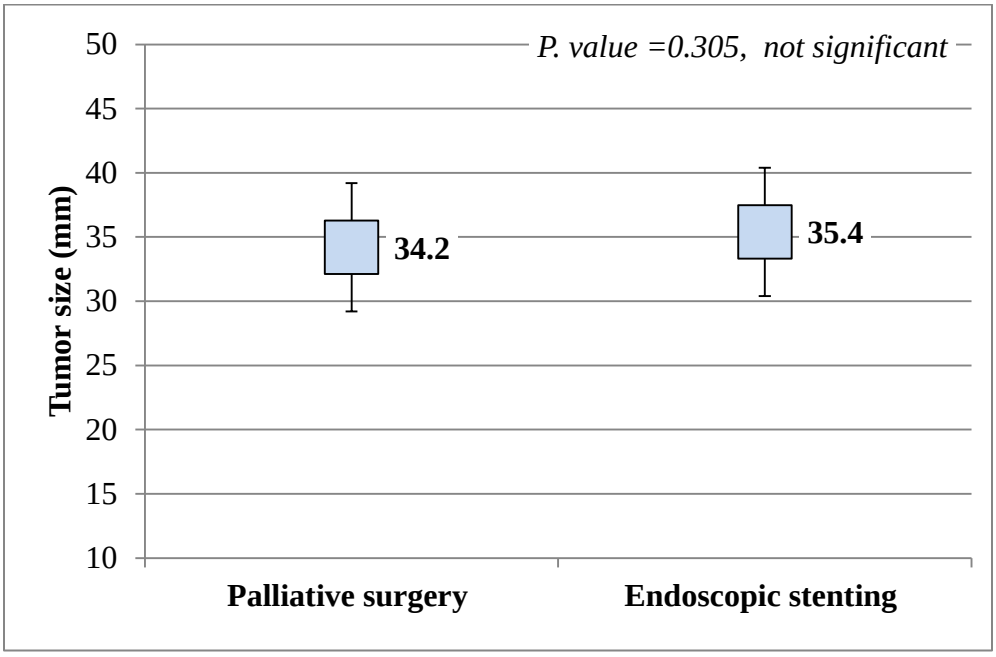

Figure 1. Comparison of mean size of tumors in both studied groups

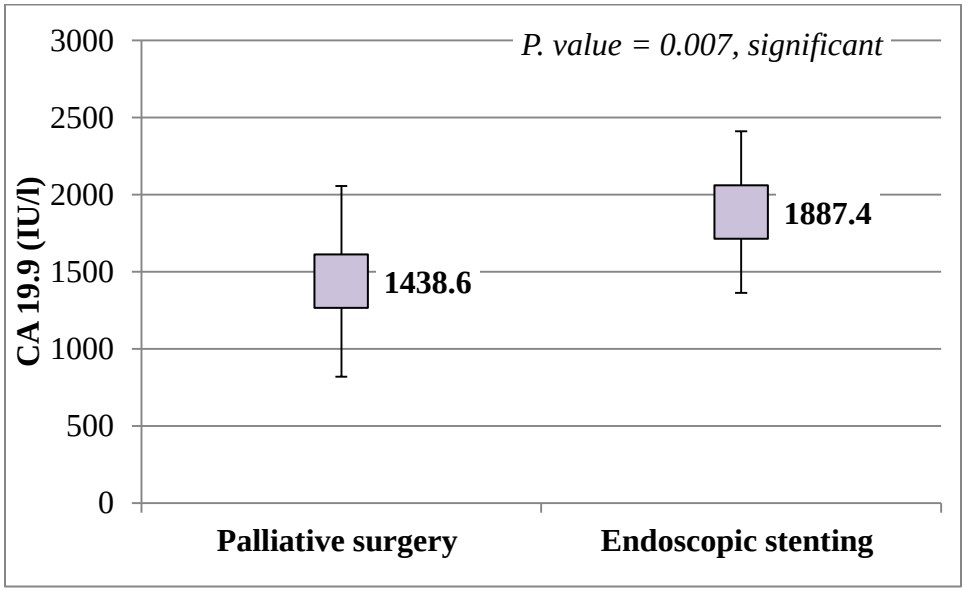

Figure 2. Comparison of mean CA-19.9 in both studied groups

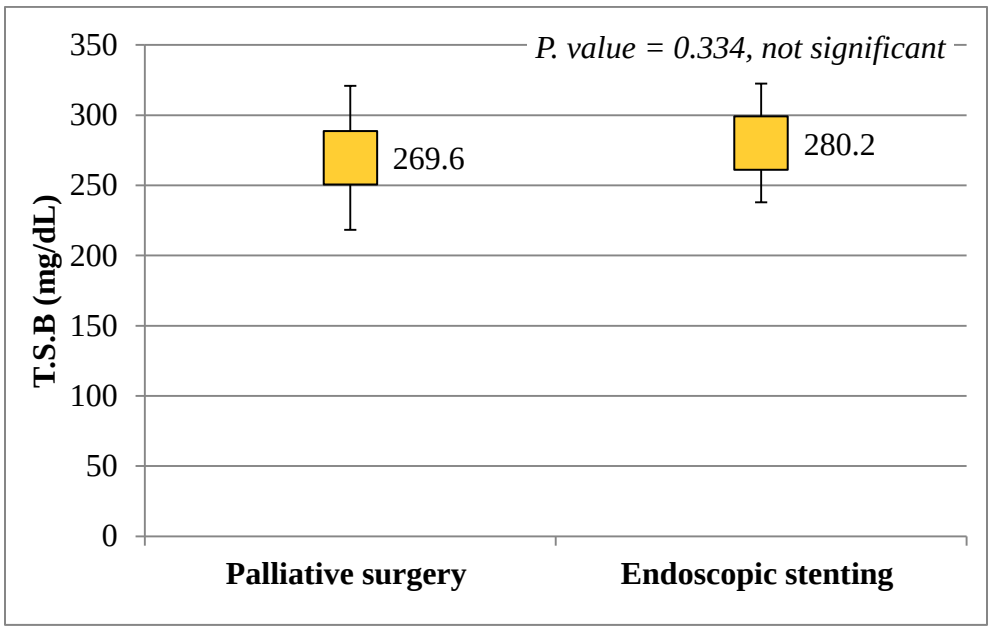

Figure 3. Comparison of mean TSB in both studied groups

Table 2. Post intervention early complications and 30-day mortalities of the studied group

Variable	Palliative surgery		Endoscopic stenting		P. value
	No.	%	No.	%	
Complication					
• Sepsis	16	43.2	8	21.6	0.082 ns
• Bleeding	5	13.5	7	18.9	0.752 ns
• Stent blockage or bypass	-	-	4	10.8	-
Thirty-day mortality	2	5.4	6	16.2	0.261 ns

ns: not significant

Table 3. Late complications, readmission and mortalities after 30 days of the studied groups

Variable		Palliative surgery		Endoscopic stenting		P. value
		No.	%	No.	%	
Complication	Cholangitis	3	8.1	2	5.4	0.894 ns
	Abdominal pain	4	10.8	4	10.8	1.000 ns
	Recurrent Jaundice	0	0.0	10	27.0	**0.002 sig**
	G.O.O.	0	0.0	3	8.1	0.238 ns
Readmission		5	13.5	17	45.9	**0.005 sig**
Mortality		0	0.0	3	8.1	0.238 ns

ns: not significant, sig: significant, GOO: Gastric outlet obstruction

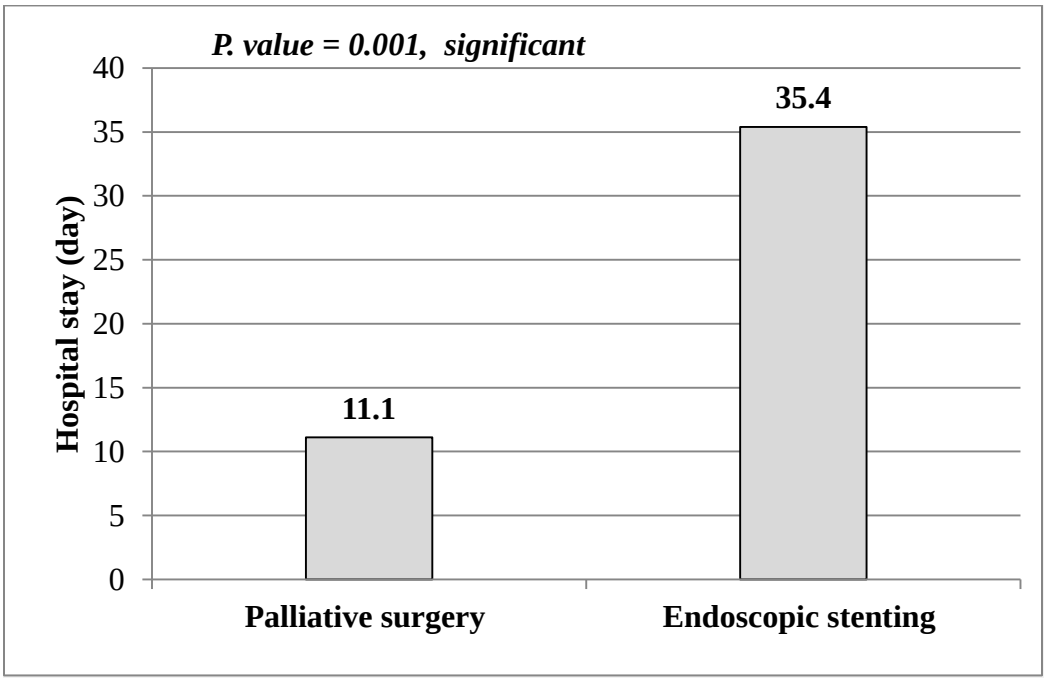

Figure 4. Comparison of duration of hospital stay in both studied groups

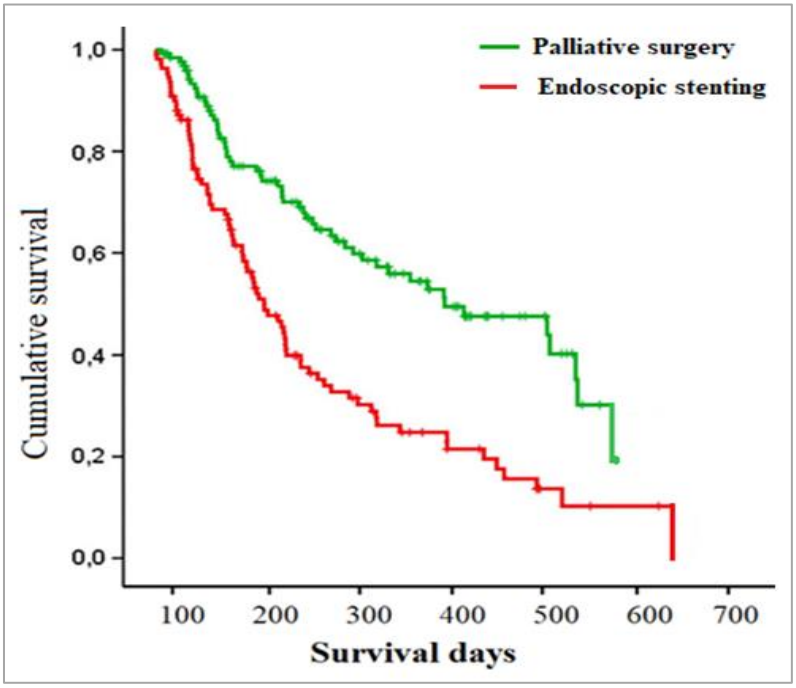

Figure 5. Survival after palliative surgery and Endoscopic stenting (P. value < 0.05, significant)

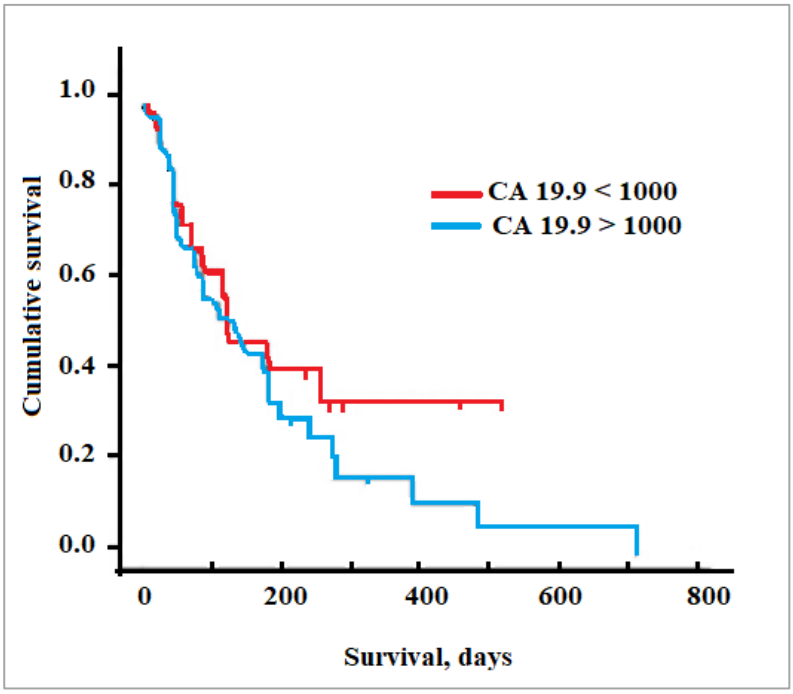

Figure 6. Survival and preoperative CA 19.9 levels (P. value < 0.05, significant)

4. DISCUSSION

In majority of patients with pancreatic cancer, the diagnosis, unfortunately made at non-resectable advanced stage and jaundiced at presentation. With locally advances disease in such patients, method of palliation, surgical bypass or endoscopic placement of biliary endoprosthesis are the common two palliation methods (22), however, which method is the best or superior is still under debate and the results of previous clinical trials are sometime conflicting (23). In developing countries, surgical bypass is preferred due to different factors; in unresectable head pancreatic cancer, metal stenting has shown to be associated with longer patency and superior cost-effectiveness from one side, from the other side, they are expensive to be routinely used and recommended in these countries. On the other hand there still a debate about the outcome in patients who received biliary endoprothesis compared to bypass surgeries as palliative treatment of obstructive jaundice (23,24).

In the present study, both groups were almost matched for age and gender. This matching is necessary to exclude any confounding effect of these variables on the outcome of the study, matching is recommended by epidemiological literatures to control confounders (25).

Regarding the tumor size, no significant difference was found, regarding the CA-19.9 it was significantly lower in patients underwent surgical bypass, while TSB was not significantly different between both groups, these findings were not unexpected, due to well randomization and assignment of patients into the treatment groups.

The higher levels of CA 19.9 and TSB were expected due to nature of the disease as these two parameters sometimes considered as predictors of disease stage. In previous study conducted in 2019, elevated CA 19.9 has shown to be associated with invasiveness of cancer and worse survival. Also a value of more than 178 UI/ml suggested resectability of pancreatic adenocarcinomas (26–28). In our study we performed further analysis to assess the influence of CA 19.9 on the survival of patients, we found that CA 19.9 level of < 1000 significantly associated with higher survival rate compared to patients with higher levels of CA 19.9 of > 1000, this finding agreed that reported in previous studies that found an inverse association between preoperative CA 19.9 levels and survival of patients with pancreatic cancer (29,30).

From other point of view, hyperbilirubinaemia is common presentation of patients with

unresectable pancreatic head adenocarcinomas. this hyperbilirubinaemia, in 70%-80% of patients is due to obstruction of the central bile duct, this obstruction and higher levels of TSB usually complicate the management and worsen the outcome because it may cause cholangitis and recurrent hospitalization (31).

In the present study, the early complication included, sepsis and bleeding in both groups, however, sepsis was more frequent in palliative bypass group than endoscopic stenting group, nonetheless the difference was statistically insignificant, (P>0.05). Bleeding was more frequent in endoscopic stenting group and the difference was also not significant, the non-statistical significance could be attributed to small sample size, despite this non-significant difference, the clinical higher frequency of sepsis in bypass group and higher bleeding frequency in endoscopic stenting group is clinically significant, these findings agreed that reported in previous studies; Scott et al. found that sepsis occurred in 43.5% of surgical bypass group compared to 21.2% in endoscopic stenting group, conversely, Scott et al. found that bleeding was also more frequent surgical bypass group than endoscopic stenting group in a rate of 34.9% vs. 15.1%, respectively, however, in both complications no statistical significant difference was found by Scott et al. (22). From other point of view, stent blockage or bypass occurred in 10.8% of our endoscopic stenting group, this complication is not uncommon in such procedure. Sunpaweravong et al. (32) stated that stent blockage is common complication in patients treated with endoscopic stenting and this complications represented the most common cause of recurrent jaundice, on the other hand, Sunpaweravong et al. documented a median time of patency of 3 months but a 22 blockage in 15 patients were occurred (32).

Furthermore, in the present study we found a higher Thirty-day mortality in endoscopic stenting group than the surgical bypass group. This finding, supported the earlier reported findings; , Nuzzo et al. (33)documented higher complication rates and poor quality of life in stenting group, moreover, Santagati et al. (33) reported lower frequency of complications and less mortalities in surgical bypass patients compared to stented patients, these findings supported the evidence that prefer the surgical bypass than stenting method and make a strong believe that surgical bypass is superior to endoscopic stenting with regards to the effectiveness, late complication, survival and better outcome, particularly in

developing countries (24,32).

In our study we found that overall survival was significantly better in patients underwent surgical bypass compared to stenting group, however, the precise conclusion about this improvement in survival is still not well identified and needs further assessment, therefore, surgical bypass should be considered as an important option in palliation of patients with pancreatic head adenocarcinomas. The lower survival rates in our patients underwent endoscopic stenting could be attributed to the following factors; firstly, it is possibly patients treated with endoscopic stenting had higher burden of occult tumor than those treated with bypass surgery. Secondly, the conservative policy of our selection to the patients, where patients with distant metastasis were excluded, on the other hand, recurrent jaundice that responsible for more readmission and worsen the prognosis could contribute for lower survival rate in stented patient as hyperbilirubinaemia itself associated with poor outcome and lower survival rate due to its contribution to cholangitis and recurrent hospitalization (31).

According to the evidence based studies and aforementioned literatures, the importance of metallic stenting remains to be investigated with regard to its effectiveness compared to surgical bypass, because despite its higher cost, than conventional stents, but they had longer patency despite they may occluded by tumor itself when ingrowth or outgrowth occur (22). From other point of view, some authors established that the rate of technical success and efficacy are similar in both approaches; surgical bypass and metal stenting, but in term of morbidity and duration of hospitalization, are lower with endoscopic stenting, hence, those authors, did not prefer a method to the other because each has its advantage and disadvantage as they stated. On the other hand, some authors documented better outcome and improved quality of life at 30 days with lower cost with endoscopic stenting treatment (34–37).

5. CONCLUSIONS

According to the findings of our study, we can concluded that pancreatic head adenocarcinoma most commonly presented in advanced unresectable stage. Surgical bypass palliation and endoscopic metal stenting both are effective for palliation of patients with this

disease. However, Surgical bypass palliation associated with low rates of late complications s, readmission and lower mortality rates. Surgical bypass palliation was associated with higher overall survival rate. The Preoperative higher level of CA 19.9 of less than 1000 was associated with better survival and can be useful predictor in assessment of patients with pancreatic head adenocarcinoma. We recommend performing surgical bypass as palliation in patients with pancreatic head adenocarcinoma taking into account the well selection of patients who are fit for this procedure and this could help to improve the prognosis and survival. However, further studies still needed with larger sample size and multiple centers for more precise evaluation.

Ethical Clearance : The study protocol approved by the Iraqi Ministry of health-scientific committee. Verbal and Signed consents obtained from all patients. Data collection was in accordance with the World Medical Association Declaration of Helsinki, 2013, for the ethical principles of researches that involve human. Data kept confidentially and patients privacy were confirmed.

Conflict of interest: Authors declared none

Funding: None, self-funded by the authors

6. REFERENCES

1. *Saad AM, Turk T, Al-Husseini MJ, Abdel-Rahman O. Trends in pancreatic adenocarcinoma incidence and mortality in the United States in the last four decades; A SEER-based study. BMC Cancer. 2018;18(1):1–11.*
2. *Latenstein AEJ, van der Geest LGM, Bonsing BA, Groot Koerkamp B, Haj Mohammad N, de Hingh IHJT, et al. Nationwide trends in incidence, treatment and survival of pancreatic ductal adenocarcinoma. Eur J Cancer. 2020;125:83–93.*
3. *Rawla P, Sunkara T, Gaduputi V. Epidemiology of Pancreatic Cancer: Global Trends, Etiology and Risk Factors. World J Oncol. 2019;10(1):10–27.*
4. *Kardosh A, Lichtensztajn DY, Gubens MA, Kunz PL, Fisher GA, Clarke CA. Long-Term Survivors of Pancreatic Cancer: A California Population-Based Study. Pancreas. 2018 Sep;47(8):958–66.*
5. *Huang J, Lok V, Ngai CH, Zhang L, Yuan J, Lao XQ, et al. Worldwide Burden of, Risk Factors for, and*

Trends in Pancreatic Cancer. Gastroenterology. 2021;160(3):744–54.

6. *Annual Statistical Report 2019. Planning Directorate, Ministry of Health/Environment, Republic of Iraq, 2019. https://moh.gov.iq/upload/upfile/ar/1070.pdf. Accessed 25 Oct 2021.*
7. *Al Alwan NAS. General Oncology Care in Iraq. In: Cancer in the Arab World. Springer, Singapore; 2022. p. 63–82.*
8. *Makar M, Zhao E, Tyberg A. Personalized Approach to the Role of Endoscopic Ultrasound in the Diagnosis and Management of Pancreaticobiliary Malignancies. J Pers Med. 2021;11(3):180-8.*
9. *Takadate T, Morikawa T, Ishida M, Aoki S, Hata T, Iseki M, et al. Staging laparoscopy is mandatory for the treatment of pancreatic cancer to avoid missing radiologically negative metastases. Surg Today. 2021;51(5):686–94.*
10. *Kaissis G, Braren R. Pancreatic cancer detection and characterization—state of the art cross-sectional imaging and imaging data analysis. Transl Gastroenterol Hepatol. 2019;4.*
11. *Lee ES, Lee JM. Imaging diagnosis of pancreatic cancer: a state-of-the-art review. World J Gastroenterol. 2014 Jun;20(24):7864–77.*
12. *Spiliopoulos S, Zurlo MT, Casella A, Laera L, Surico G, Surgo A, et al. Current status of non-surgical treatment of locally advanced pancreatic cancer. World J Gastrointest Oncol. 2021;13(12):2064–72.*
13. *Ekström A, Brun E, Eberhard J, Segerlantz M. Second-line palliative chemotherapy, survival, and prognostic factors in patients with advanced pancreatic cancer. Acta Oncol (Madr). 2021;60(12):1580–8.*
14. *Huggett MT, Ghaneh P, Pereira SP. Drainage and bypass procedures for palliation of malignant diseases of the upper gastrointestinal tract. Clin Oncol (R Coll Radiol). 2010 Nov;22(9):755–63.*
15. *Erdoğan AP, Ekinci F, Yıldırım S, Özveren A, Göksel G. Palliative Biliary Drainage Has No Effect on Survival in Pancreatic Cancer: Medical Oncology Perspective. J Gastrointest Cancer. 2022;53(1):52–6.*
16. *Jang DK, Kim J, Yoon SB, Yoon WJ, Kim J-W, Lee TH, et al. Palliative endoscopic retrograde biliary drainage for malignant biliary obstruction in Korea: A nationwide assessment. Saudi J Gastroenterol Off J Saudi Gastroenterol Assoc. 2021;27(3):173-9.*
17. *DiFronzo LA, Egrari S, O'Connell TX. Choledochoduodenostomy for palliation in unresectable pancreatic cancer. Arch Surg. 1998;133(8):820–5.*
18. *Kim EY, Lee SH, Hong TH. Palliative laparoscopic Roux-en-Y choledochojejunostomy as a feasible treatment option for malignant distal biliary obstruction. Surg Today. 2022;1–8.*

19. Kermavnar T, Guttridge C, Mulcahy NJ, Duffy E, Twomey F, O'Sullivan L. 3D printing in palliative medicine: systematic review. BMJ Support Palliat Care. 2022; e 2022;0:1–10

20. Levy MJ, Baron TH, Gostout CJ, Petersen BT, Farnell MB. Palliation of malignant extrahepatic biliary obstruction with plastic versus expandable metal stents: an evidence-based approach. Clin Gastroenterol Hepatol. 2004;2(4):273–85.

21. Ballinger AB, McHugh M, Catnach SM, Alstead EM, Clark ML. Symptom relief and quality of life after stenting for malignant bile duct obstruction. Gut. 1994;35(4):467–70.

22. Scott EN, Garcea G, Doucas H, Steward WP, Dennison AR, Berry DP. Surgical bypass vs. endoscopic stenting for pancreatic ductal adenocarcinoma. HPB Off J Int Hepato Pancreato Biliary Assoc. 2009 Mar;11(2):118–24.

23. Mintziras I, Miligkos M, Wächter S, Manoharan J, Bartsch DK. Palliative surgical bypass is superior to palliative endoscopic stenting in patients with malignant gastric outlet obstruction: systematic review and meta-analysis. Surg Endosc. 2019;33(10):3153–64.

24. Mazine K, Mohammed H, Abdelmalek O, Khalid M, Adil I, Khalid AT, et al. Surgical Bypass versus Endoscopic Stenting for Unresectable Head Pancreatic Cancer, Which Palliative Treatment Is Better in Developing Countries, Morocco as an Example. Open J Gastroenterol. 2017;7(05):154-64.

25. De Graaf MA, Jager KJ, Zoccali C, Dekker FW. Matching, an appealing method to avoid confounding? Nephron Clin Pract. 2011;118(4):c315–8.

26. Jin X, Wu Y. Diagnostic utility of clinical and biochemical parameters in pancreatic head malignancy patients with normal carbohydrate antigen 19-9 levels. Afr Health Sci. 2015 Mar;15(1):123–30.

27. Santucci N, Facy O, Ortega-Deballon P, Lequeu J-B, Rat P, Rat P. CA 19–9 predicts resectability of pancreatic cancer even in jaundiced patients. Pancreatology. 2018;18(6):666–70.

28. Ciprani D, Morales-Oyarvide V, Qadan M, Hank T, Weniger M, Harrison JM, et al. An elevated CA 19-9 is associated with invasive cancer and worse survival in IPMN. Pancreatology. 2020;20(4):729–35.

29. Duffy MJ, Sturgeon C, Lamerz R, Haglund C, Holubec VL, Klapdor R, et al. Tumor markers in pancreatic cancer: a European Group on Tumor Markers (EGTM) status report. Ann Oncol. 2010;21(3):441–7.

30. Liu L, Xu H, Wang W, Wu C, Chen Y, Yang J, et al. A preoperative serum signature of CEA+/CA 125+/CA 19-9≥ 1000 U/m L indicates poor outcome to pancreatectomy for pancreatic cancer. Int J

cancer. 2015;136(9):2216–27.

31. *Vogel A, Kullmann F, Kunzmann V, Al-Batran S-E, Oettle H, Plentz R, et al. Patients with advanced pancreatic cancer and hyperbilirubinaemia: review and German expert opinion on treatment with nab-paclitaxel plus gemcitabine. Oncol Res Treat. 2015;38(11):596–603.*
32. *Sunpaweravong S, Soontrapornchai P, Charoonratana V, Ovartlarnporn B, Khow-ean U. Endoscopic Stenting Versus Surgical Bypass in Advanced Malignant Distal Bile Duct Obstruction: Cost-effectiveness Analysis. Asian J Surg. 2005;28(4):262–5.*
33. *Nuzzo G, Clemente G, Cadeddu F, Giovannini I. Palliation of unresectable periampullary neoplasms." surgical" versus" non-surgical" approach. Hepatogastroenterology. 2004;51(59):1282–5.*
34. *Lyons JM, Karkar A, Correa-Gallego CC, D'Angelica MI, DeMatteo RP, Fong Y, et al. Operative procedures for unresectable pancreatic cancer: does operative bypass decrease requirements for postoperative procedures and in-hospital days? HPB. 2012;14(7):469–75.*
35. *Artifon ELA, Sakai P, Cunha JEM, Dupont A, Filho FM, Hondo FY, et al. Surgery or Endoscopy for Palliation of Biliary Obstruction Due to Metastatic Pancreatic Cancer. Off J Am Coll Gastroenterol | ACG. 2006;101(9): 2031-7..*
36. *Moss AC, Morris E, Leyden J, MacMathuna P. Malignant distal biliary obstruction: A systematic review and meta-analysis of endoscopic and surgical bypass results. Cancer Treat Rev. 2007;33(2):213–21.*
37. *Maire F, Sauvanet A. Palliation of biliary and duodenal obstruction in patients with unresectable pancreatic cancer: Endoscopy or surgery? J Visc Surg. 2013;150(3, Supplement):S27–31.*