

Results of surgical treatment of carcinoma of papilla of Vater

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Key words: ampulla of Vater; carcinoma; surgery; survival rates.

Summary. Adenocarcinoma is the most common malignant tumor of the ampulla, but in general, it is still rare. Therefore, these tumors are difficult to study, and most reports are of retrospective design. To evaluate immediate postoperative and long-term results, we have collected data prospectively in a specially created database on 21 consecutive patients with adenocarcinoma of the papilla of Vater, operated on at the Department of Surgery, Kaunas University of Medicine Hospital. All patients have undergone classical or pylorus-preserving pancreaticoduodenectomy.

Postoperative mortality was 4.8% and overall morbidity – 28.6%. Pancreas-associated morbidity was 14.3% in the series.

Actuarial 3-year survival among our patients was 89%.

Stage I–II patients with T1–T2 and/or N negative tumors had significantly better 3-year survival when compared with stage III–IV patients, T3–T4 and/or N positive tumors. Patients with highly or moderately differentiated tumors (G1, G2) survived better than patients with poor cell differentiation (G3), though significant difference was not achieved.

Results are satisfactory in terms of overall postoperative morbidity and mortality. Long-term survival pattern concerning T, N, and G status corresponds with other reports in literature, while the 3-year survival results are promising and speaks in favor of our surgical strategy.

Introduction

The anatomy of the ampulla of Vater is very complex. It consists of three different epithelia (bile duct, pancreatic duct, and duodenum). Adenomas are considered as precancerous lesions, and they usually occur in the fifth-sixth decade of life. There is evidence supporting adenoma-carcinoma sequence of neoplastic lesions of ampulla of Vater (1–3). The frequency of malignant lesion in an adenoma of the papilla is about 26% (4). In postmortem studies, carcinomas of papilla of Vater have been reported in 0.2% of cases (5).

Through increased use of endoscopy, ampullary tumors are more frequently recognized. Differentiation of adenocarcinoma of the pancreas from ampullary tumors is also important considering better prognosis for long-term survival in the latter group. It is generally agreed that adenocarcinoma of papilla of Vater should be removed by partial pancreaticoduodenectomy, whereas local ampullectomy with local lymphadenectomy should be reserved for pTis and pT1N0M0G1 or G2 tumors (4).

Adenocarcinoma is the most common malignant tumor of the ampulla, but in general, it is still rare. That is why these tumors are very difficult to study,

and most reports considering ampullary tumors are of retrospective design.

To evaluate immediate postoperative as well as long-term results, we have collected data prospectively in a specially created database on 21 consecutive patients with adenocarcinoma of the papilla of Vater who had been operated on at the Department of Surgery, Kaunas University of Medicine Hospital. We have evaluated preoperative clinical data, pathology reports, tumor stage according to the International Union Against Cancer (UICC), postoperative morbidity, mortality, and long-term follow-up results.

Patients and methods

Between January 1, 1999, and May 30, 2003, 21 patients with adenocarcinoma of the papilla of Vater were operated on. In this group, 5 patients were male and 16 were female. The median age of all studied patients was 66 years (interquartile range 62–72). The median age of men was 72 years (interquartile range 66–73), and the median age of women was 66 years (interquartile range 59.5–70.5). Stage I and stage II tumors were predominant in female patients but without statistical difference (Table 1).

Table 1. Demographic data of patients operated on for ampullary carcinoma

Gender	Age, years		Tumor stage (UICC)	
	median	range	stage I–II	stage III–IV
Male	72	65–73	2	3
Female	66	49–74	12	4
Overall	66	49–74	14	7

UICC – the International Union Against Cancer.

Surgical techniques

All 21 patients underwent major resection for malignant disease – Whipple procedure or pylorus-preserving partial pancreatoduodenectomy. The lymph-node dissection in all cases was performed in pursuance of D2 extent as it is performed in case of adenocarcinoma of the head of the pancreas.

Definition of surgical principles

Radical pancreatoduodenectomy was defined at our department as a resection of the head of the pancreas, duodenectomy, and a resection of the initial segment of jejunum; lymph node dissection, including anterior and posterior lymph nodes of the pancreatic head, supraduodenal, common and proper hepatic artery, hepatoduodenal ligament, and lymph nodes to the right of the superior mesenteric artery; cholecystectomy with an en-block resection of the common bile duct; retroportal, retropancreatic fatty tissue dissection plus dissection of lymph-nodes from the interaortocaval space with following reconstruction using the first jejunal loop, end-to-side pancreaticojejunostomy, end-to-side hepaticojejunostomy without internal stents or other intraluminal decompressing or draining devices (6).

Whipple procedure consisted of Billroth II resection of the stomach with sequential retrocolic gastroenteroanastomosis. Additional Braun entero-enteroanastomosis was never applied.

Pylorus-preserving pancreaticoduodenectomy (PPPD) consisted of the resection of duodenum approximately 3 cm below pylorus and sequential end-to-side duodenojejunal anastomosis in front and above the transverse colon using one-layer running fine (4/0 or 5/0) resorbable monofilament suture. Thus, the latter anastomosis is being located in some distance from pancreaticojejunostomy with a flap of omentum interposed between the two.

R0 and R1 resections were defined as stated elsewhere (4). Definitions of pancreas-related morbidity were described by our group earlier (7).

Statistical analysis

Data were expressed as median and interquartile range. Survival analysis was performed by the method of Kaplan-Meier. Differences in survival rates between patient subsets were compared by log-rank test. Significance was accepted at the 5% level.

Results

Twenty-one patients with malignant tumor of the papilla of Vater had undergone radical pancreatoduodenectomy, and 61.9% (13 of the 21 patients) of them were older than 65 years of age. Median serum bilirubin level of the cohort at presentation was 79 $\mu\text{mol/L}$ (range 10–271 $\mu\text{mol/L}$). Of them, 57.1% (12 of the 21 patients) were not jaundiced, whereas 42.9% (9 of the 21) of patients presented with serum bilirubin level exceeding 100 $\mu\text{mol/L}$. In 4 of these patients, preoperative biliary drainage was performed because of excessive serum bilirubin level and markedly impaired cardiac function, requiring medical management prior to surgery. All these patients were aged more than 65 years.

Diagnostic tests performed were contrast-enhanced CT scan and endoscopic retrograde cholangiopancreatography (ERCP) with multiple biopsies before surgery.

Final pathology report stated that the diagnosis in all 21 patients was adenocarcinoma of the papilla of Vater (Table 2). According to pTNM stages (UICC, 1997), there were 4 (19.1%) stage I, 10 (47.6%) stage II, 5 (23.8%) stage III, and 2 (9.5%) stage IV patients. Distribution of patients according to cell differentiation is presented in Table 3. In 28.6% of cases (6 of 21 patients), lymph nodes were involved (pN1). In 19 (90.5%) patients, pylorus-preserving pancreatoduodenectomy was performed and R0 resection was accomplished.

Two patients in stage IV have undergone standard Whipple procedure. In one of these patients, partial pancreatoduodenectomy was classified as R1 resection, and was confirmed by postoperative pathology report as showing malignant cell invasion into retroperitoneal tissues at the plane of resection.

Table 2. Tumor (T) classification in patients with ampullary carcinoma

Tumor classification	Number of patients (%)	Node involvement (negative/positive)
T1	4 (19)	4/0
T2	9 (42.9)	8/1
T3	6 (28.6)	2/4
T4	2 (9.5)	1/1

Table 3. Distribution of patients according to cell differentiation (G)

Cell differentiation	Number of patients	%
G1	3	14.2
G2	9	42.9
G3	9	42.9

The median number of lymph nodes procured during lymphadenectomy was 17. Among the patients who underwent radical pancreatoduodenectomy, none presented with distant metastases at surgery.

None of the patients have received postoperative chemotherapy.

Postoperative mortality after pancreatoduodenectomy was 4.8% (1 of the 21 patients). The overall

morbidity rate was 28.6%. Pancreas-associated morbidity (pancreatic fistula and peripancreatic sepsis) was 14.3%. Relaparotomy was needed in 2 (9.5%) patients due to intraabdominal hemorrhage. We observed a low rate of delayed gastric emptying postoperatively (1 of 21 patients, 4.8%).

The median follow-up of patients after radical pancreatoduodenectomy because of ampullary tumor was 21.1 months, ranging from 6.3 to 55 months. The overall 3-year actuarial survival among the patients with carcinoma of papilla of Vater was 89%. A 3-year actuarial survival among the patients with the stage I and stage II disease was 100%. Patients diagnosed with stage III and IV disease had an actuarial 3-year survival of 67%, the difference between groups being significant, $P=0.046$ (Fig. 1). We tested 3-year survival according to T (tumor) classification, grouping T1 and

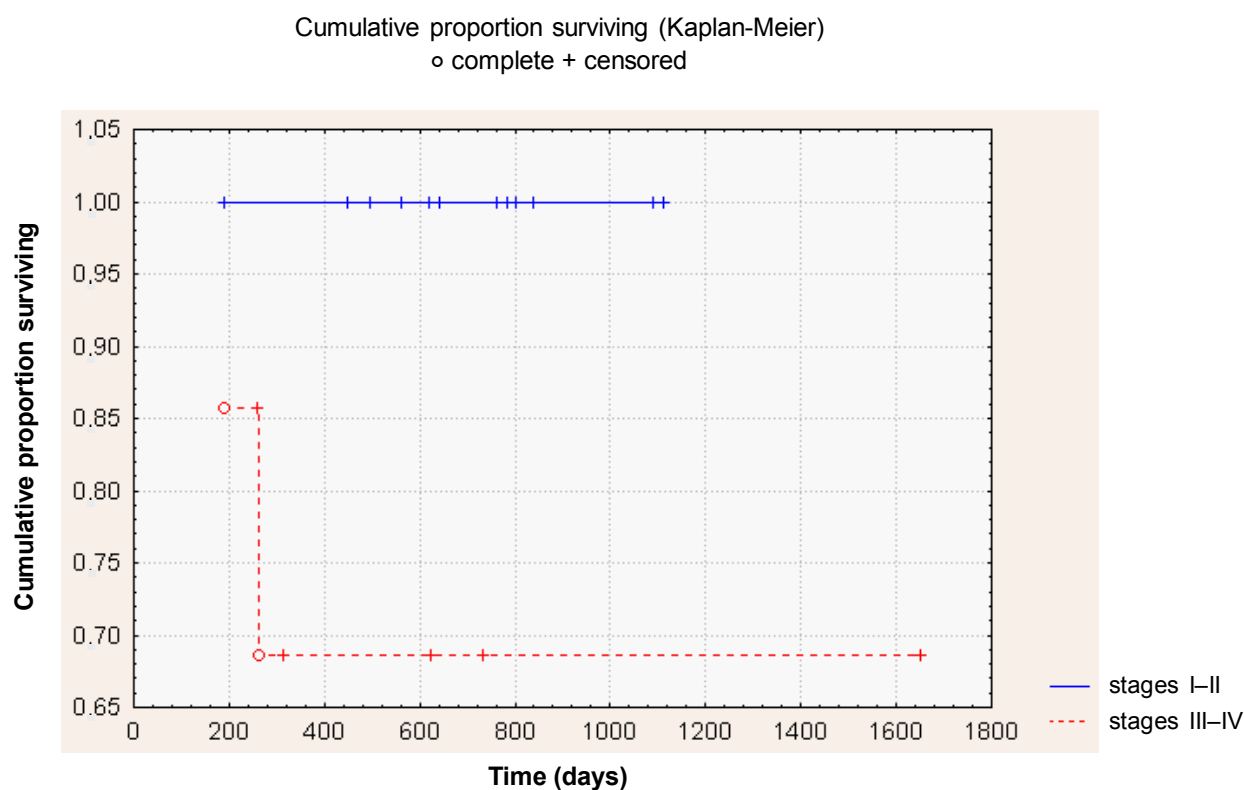


Fig. 1. Three-year survival between the patients with stage I and stage II tumor was significantly different ($P=0.046$) when compared with stage III and stage IV cancer patients

T2 cases as one group and T3–T4 as the other. The rationale for the grouping was presence (T3,4) or absence (T1,2) of pancreatic tissue infiltration by the tumor. Three-year survival in the T1,2 group was 100%, whereas in more advanced cases (T3,4) survival was 68%. Log-rank test showed significant differences between the groups ($P=0.047$) (Fig. 2). Grouping the patients according to N (node) value to positive (N1) and negative (N0) showed significant difference ($P=0.024$) (Fig. 3). Patients who had ampullary tumors with high or moderate differentiation of cells (G1 and G2) experienced slightly better survival than the patients with poorly differentiated tumors (G3); however, significant difference was not achieved ($P=0.132$) (Fig. 4). Establishing gender differences, our data show that overall 3-year survival was higher in women who underwent radical pancreatoduodenectomy for ampullary cancer than in men, though not significantly (93% vs. 75%, respectively; $P=0.28$) (Fig. 5).

Discussion

Ampullary cancer has the best resectability rate and the best prognosis among periampullary cancers. It can be explained by earlier presentation because of

anatomic location of tumor and in part by different biological aggressiveness with regard to pancreatic adenocarcinoma. Carcinoma of the ampulla exhibits differences in macroscopic growth pattern showing lower frequency of local infiltration, vascular or neural invasion when compared to pancreatic adenocarcinoma (8). More extensive use of endoscopic retrograde cholangiopancreatography also contributed to earlier and more precise diagnosis of this particular tumor. Though magnetic resonance cholangiopancreatography (MRCP) may take over the diagnostic role of ERCP, direct visualization of the papilla and possibility to obtain multiple biopsies under direct visual control remains unsurpassed.

Pancreatoduodenectomy is the procedure of choice in case of cancer of papilla of Vater though still bearing 2% to 5% mortality and substantial morbidity of 30–40%.

Our data show similar results. The grounds of delayed gastric emptying are still debated, and few hypotheses have been proposed (9–12). Quite a low rate of delayed gastric emptying in our series might be attributed to the pattern of reconstruction of gastrointestinal tract.

Some authors have been advocating a local ex-

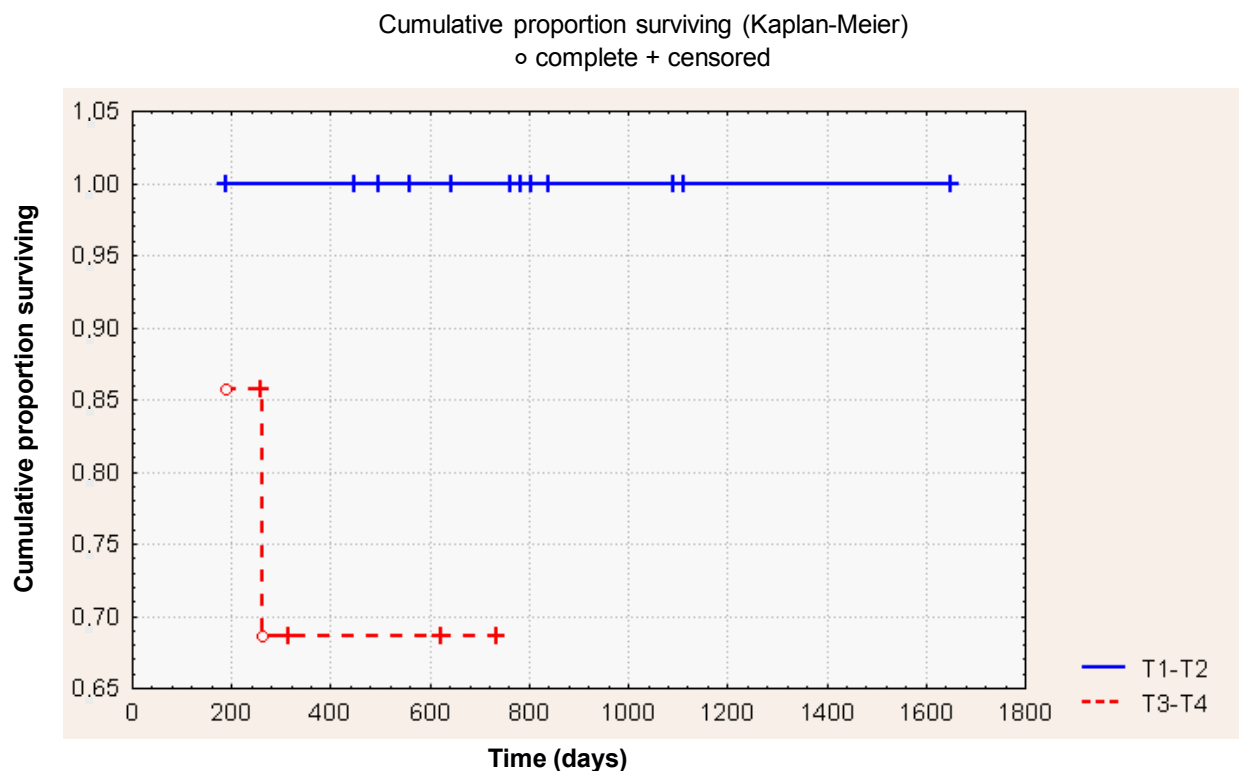


Fig. 2. Testing 3-year survival according to T (tumor) classification, grouping T1 and T2 cases as one group and T3–T4 as the other

Log-rank test showed significant differences between the groups ($P=0.047$).

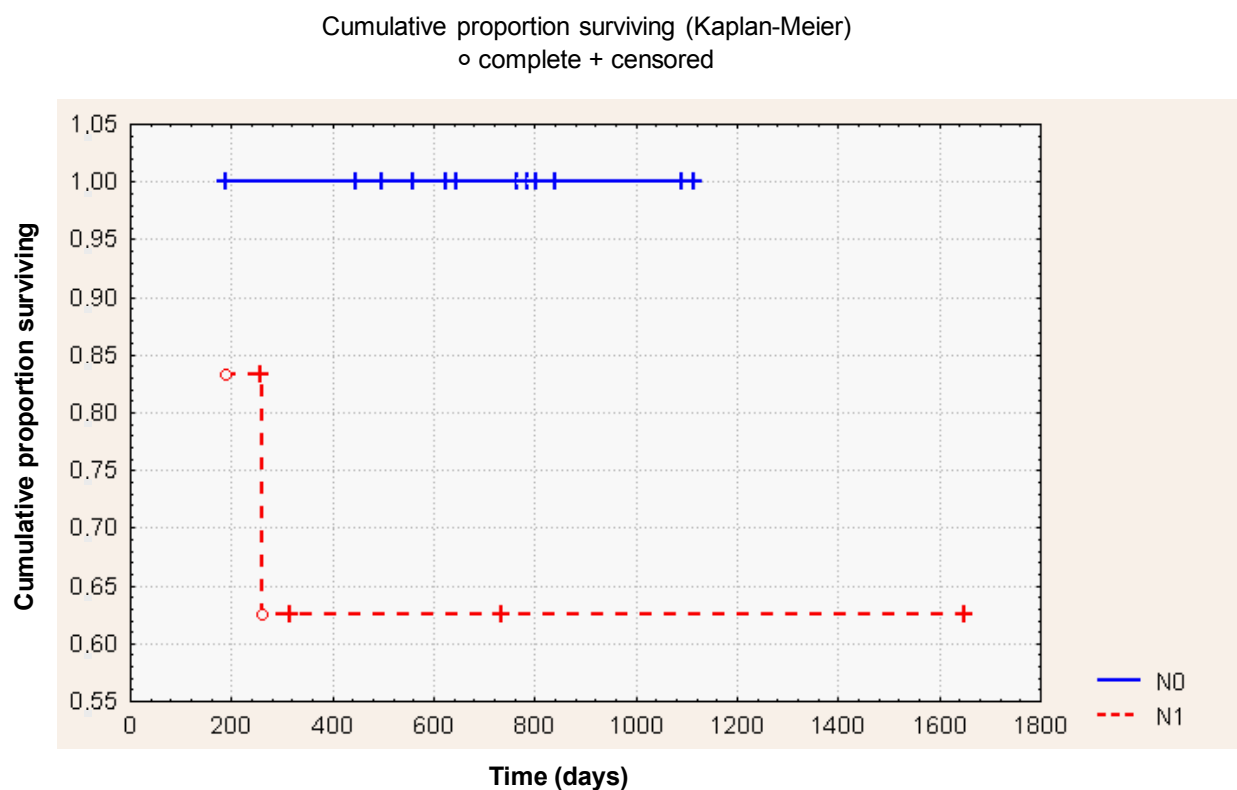


Fig. 3. Grouping the patients according to N (node) value to positive (N1) and negative (N0) showed significant difference ($P=0.024$)

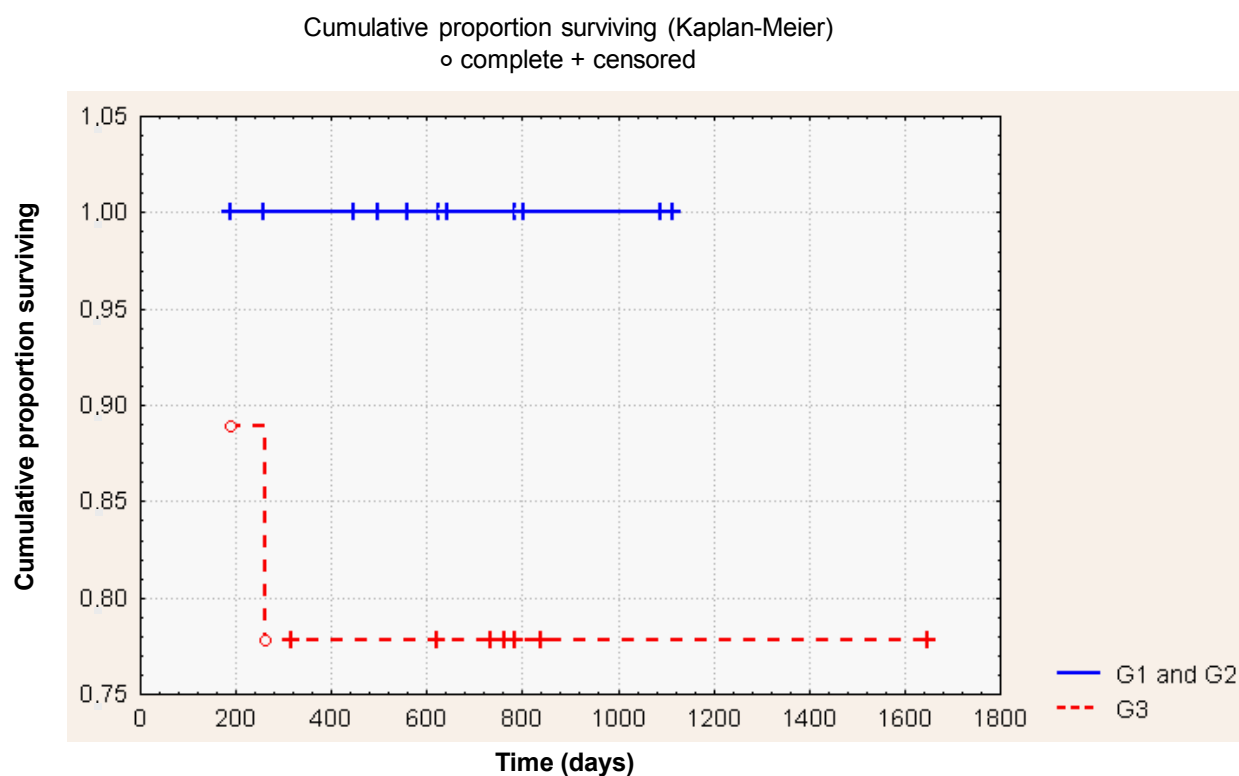


Fig. 4. Patients who had ampullary tumors with high or moderate differentiation of cells (G1 and G2) survived better than patients with poor cell differentiation (G3), though significant difference was not achieved ($P=0.132$)

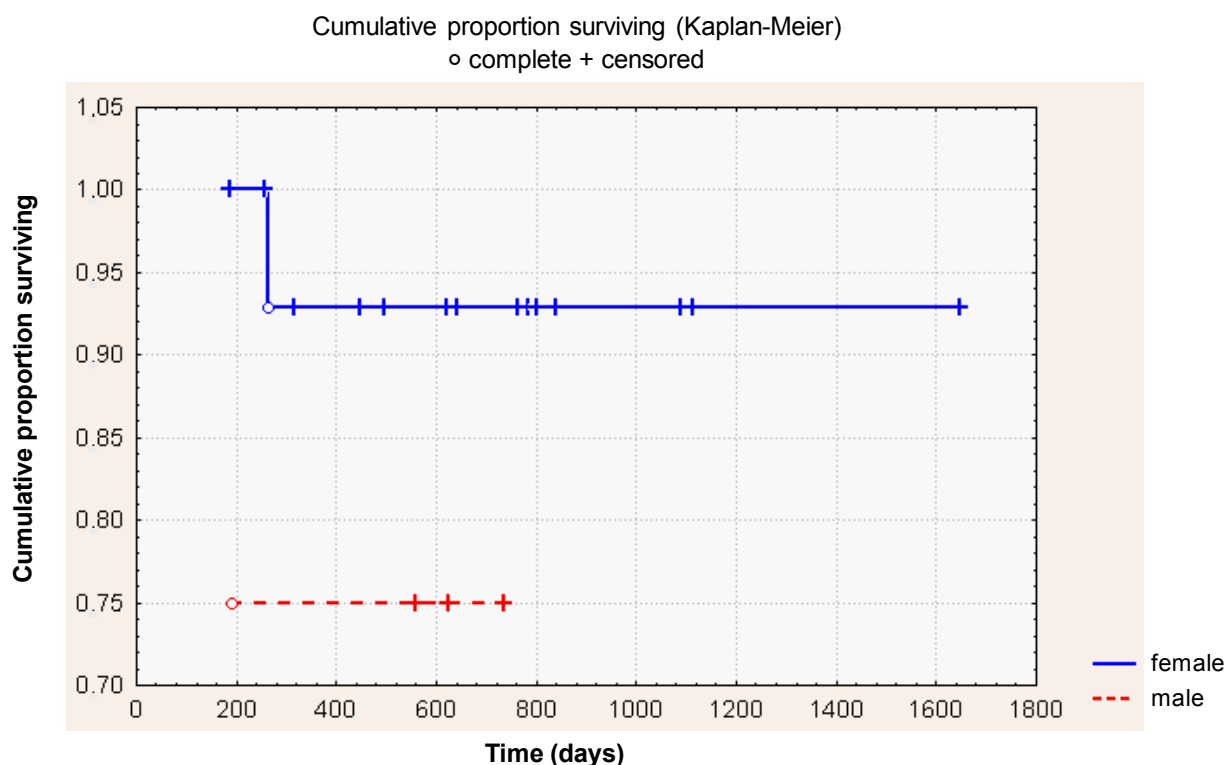


Fig. 5. Overall 3-year survival was higher in women who underwent radical pancreatoduodenectomy for ampullary cancer than in men though significant difference was not achieved ($P=0.28$)

cision for localized (T2N0 or less) and well-differentiated ampullary carcinomas, and there are studies reporting favorable results for local excision of non-advanced ampullary carcinoma (13, 14).

Meanwhile others, because of uncertainty of reliable preoperative diagnosis and extent of malignancy, have proposed to consider all ampullary epithelial neoplasms potentially malignant and to treat them by radical pancreatoduodenectomy (15–17), stressing key importance of adequate lymph node dissection (18).

We have favored the latter approach on the basis that local recurrence of tumor is much rarer after pancreatoduodenectomy than after local excision of even small ampullary lesion (19,20) and while morbidity (28.6%) and mortality (4.8%) rates at our department are reasonable and stay similar to those reported in the literature (4, 21).

The differences of survival in patients grouped based on lymph node status and infiltration to pancreatic tissue are indicative to the prognosis of the disease. It has been shown that in an “early” ampullary cancer, invading mucosa or muscle of Oddi sphincter, no lymph node metastases have been observed, whereas invasion into submucosa of duodenum and deeper layers have resulted in 63% of regional lymph node involvement (22).

The number of positive nodes in superior mesen-

teric artery lymph node group has also increased with the increasing T stage suggesting extension of the lymphatic spread from the posterior pancreaticoduodenal to the superior mesenteric nodes (23).

Beger and co-workers (4) have reported 60% lymph node metastasis in patients with T3 and T4 carcinoma of papilla of Vater, whereas only 22% were observed in T1–T2. Our data revealed positive lymph nodes in 62.5% of patients with T3–T4 carcinoma, whereas only 7.7% were present in patients with T1–T2 carcinoma of papilla of Vater. It has been suggested on this basis that pancreatic invasion of the ampullary tumor (T3–4) indirectly indicates the status of regional lymph nodes. Therefore, extended dissection of lymph nodes is being applied at our department when performing radical pancreatoduodenectomy for ampullary tumors. However, today we still lack controlled clinical data on the impact of extended lymph-node dissection on long-term results.

The published series show 1-year survival to be more than 80%, 3 year survival – 60%–70%, and 5-year survival around 50% (24, 25). In recently published series with R0 resection in T1 patients, a 5-year survival was 100% (26). It is evident that R0 resection is obligatory in order to achieve similar long-term results. On the other hand, there is still not enough

evidence confirming more extensive lymph node dissection translates directly into prolonged survival for patients with periampullary tumors (27).

Conclusion

We find our results satisfactory in terms of overall postoperative morbidity and mortality. The lower rate

of delayed gastric emptying may be attributed to the pattern of gastrointestinal tract reconstruction and meticulous surgical technique. Long-term survival pattern concerning T, N, and G status corresponds with other reports in literature, while the 3-year survival results are promising and speaks in favor of our surgical strategy.

Didžiojo dvylikapirštės žarnos spenelio karcinomos chirurginio gydymo rezultatai

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Raktažodžiai: didysis dvylikapirštės žarnos spenelis, vėžys, chirurginis gydymas, išgyvenimas.

Santrauka. Adenokarcinoma yra dažniausias dvylikapirštės žarnos didžiojo spenelio piktybinis navikas, tačiau kitų piktybinių navikų atžvilgiu tai yra retas navikas. Tai apsunkina šių navikų tyrinėjimus, o publikuojami moksliniai darbai dažniausiai yra retrospektyviojo pobūdžio. Siekiant išanalizuoti ankstyvuosius ir vėlyvuosius gydymo rezultatus, mes savo sukurtoje duomenų bazėje prospektyviai surinkome duomenis 21 ligonio, operuoto Kauno medicinos universiteto klinikų Chirurgijos skyriuje dėl *papilla Vateri* adenokarcinomos. Viesiems ligoniams buvo atlikta pankreatoduodeninė rezekcija.

Pooperacinis mirštamumas buvo 4,8 proc. Komplikacijų radosi 28,6 proc. atvejų, dėl kasos pažeidimo radosi 14,3 proc. komplikacijų. Apskaičiuotas trejų metų išgyvenimas – 89 proc.

Ligoniai sirgę I ir II stadijos vėžiu, kurių navikas buvo klasifikuojamas T1 ir T2 kategorijomis ir (ar) buvo nepažeisti limfmazgiai (N0), išgyveno žymiai ilgiau nei ligoniai, sirgę III–IV stadijos vėžiu, kurių navikas buvo klasifikuotas T3 ar T4 ir (ar) buvo pažeisti limfmazgiai (N1). Ligoniai, kurių navikų ląstelės buvo gerai ar vidutiniškai diferencijuotos (G1 ar G2), išgyveno ilgiau nei ligoniai, kurių navikai buvo diferencijuoti (G3), tačiau reikšmingo išgyvenimo skirtumo nenustatėme.

Ankstyvieji (pooperacinis mirštamumas, komplikacijos) ir vėlyvieji (trejų metų išgyvenimas) dvylikapirštės žarnos didžiojo spenelio adenokarcinomos chirurginio gydymo rezultatai yra patenkinami. Išgyvenimo priklausomumo nuo naviko stadijos ir naviką charakterizuojančių kategorijų (T, N, G) tendencijos atitinka kitų autorių publikuotus analogiškus duomenis. Bendrasis trejų metų išgyvenimas po chirurginės operacijos nuteikia optimistiškai ir rodo mūsų gydymo strategijos pagrįstumą.

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