



PROGNOSTIC IMPACT OF THE NUMBER OF POSITIVE LYMPH NODES AND LYMPH NODE RATIO ON THE OUTCOME OF PATIENTS AFTER RESECTION OF PANCREATIC ADENOCARCINOMA

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ABSTRACT

Introduction: The presence of metastases in the lymph node in pancreatic adenocarcinoma is considered to be a factor that affects the survival of patients after resective surgery. The aim was to examine the effect of the number of positive lymph nodes and the lymph node ratio (LNR) on the outcome of patients after pancreatic carcinoma resection.

Methods: A retrospective study was performed at the Department of Digestive Surgery, Clinical Center of Serbia, Belgrade, including 82 patients treated with radical surgery for pancreatic carcinoma (PC).

Results: Negative lymph nodes had 28 patients, whereas 54 (65.5%) had positive lymph nodes. Median survival of all patients was 14 months. Patients with two or more metastatic lymph nodes had worse survival rate compared to patients with 0 or one lymph node ($p=0.007$), while individuals with $LNR \geq 0.2$ had worse outcome than patients with $LNR < 0.2$ ($p=0.049$). According to our results factors associated with poorer survival were R1 surgical margin status ($p=0.049$) and the presence of 2 or more metastatic lymph nodes ($p=0.015$). Independent predictor of survival rate in our study were presence of ≥ 2 metastatic lymph nodes in patients with PC ($p=0.026$).

Conclusion: The number of positive lymph nodes is more important prognostic factor than LNR in patients with resection of pancreatic carcinoma. Patients with two or more positive lymph nodes had a significantly shorter survival than those without positive or with one positive lymph node.

KEYWORDS : pancreatic adenocarcinoma, metastasis, lymphadenectomy, lymph nodes, lymph node ratio

INTRODUCTION:

Pancreatic cancer (PC) presents the malignancy with the highest lethality in human population with the overall survival rate of 5-8% [1,2]. Although surgical resection is the only form of therapy that offers prolonged survival, only a relatively small percentage of patients diagnosed with pancreatic cancer are candidates for resection [3]. Nevertheless, even after surgical treatment of PC five year survival of these patients is not more than 20% [4-6].

The presence of metastasis in resected lymph nodes (LN) is considered to be a prognostic factor in patients with resected pancreatic adenocarcinoma. Numerous studies have shown that survival rate of patients with metastases in regional lymph nodes is lower compared to patients whose lymph nodes were negative [7-11]. Several studies have shown that patients with metastases in regional lymph nodes (N1) have a median overall survival of one year [9-12]. These patients compared with patients without regional lymph node metastases have significantly lower five year survival outcome [12,13]. Results of some studies suggest that the number of positive lymph nodes and lymph node ratio (LNR – ratio of positive and total resected lymph nodes) could represent better predictors of postoperative outcome compared to the status of regional lymph nodes [14-17]. The aim of this study was to investigate the impact of positive lymph nodes and LNR on the outcome of patients after pancreatic carcinoma resection.

METHODS:

Demographic and clinical data of 82 patients with PC was obtained from medical histories at the Department of Digestive Surgery, Clinical Center of Serbia. All of the included patients in the study underwent radical surgery for PC in the five year period of 2010-2015, with histopathological confirmation of adenocarcinoma. The exclusion criteria were PC patients that died in the first 30 days of surgery.

According to the number of positive lymph nodes, PC patients were divided into three groups: with negative lymph nodes, with 1 positive and with 2 or more positive lymph nodes. LNR was assessed by dividing the number of positive lymph nodes and the total number of removed lymph nodes. Based on the values of LNR, patients were also divided into groups with $LNR=0$, $LNR=0-0.2$ and $LNR \geq 0.2$. Survival analysis was performed using information obtained by telephone interview, defining the period of time that has passed from the surgery until death or up to the date of the interviews conducted for patients who survived.

Statistical analysis was performed by the statistical software package SPSS 20.0 for Windows (SPSS, Inc, Chicago, IL, USA). Methods of descriptive and analytical statistics were used. Survival curves were constructed by Kaplan-Meier method, while the differences in outcome were assessed using univariate log-rank (Mantel-Cox) test. Univariate analysis using the Cox proportional hazards model identified factors associated with poorer outcome. Multivariate analysis comprising factors that revealed significant associations during univariate testing was conducted. For all statistical analyses a $p \leq 0.05$ was required to reject the null hypothesis.

RESULTS:

Out of 82 patients included in the study, 38 (46.3%) were male and 44 (43.7%) were female. The average age of patients was 61 years (range 40-79). The most common tumor location of PC was the head of the pancreas (51.2%), while less frequent were periampular region (26.8%), the body and tail of the pancreas (22.0%). Most patients underwent cephalic duodenopancreatectomy (78.0%), while in other cases distal pancreatectomy (22%) was performed. Resection of blood vessels – portal vein, superior mesenteric vein and hepatic artery was performed in 6 (7.3%) patients. The margins of PC resection in 34 (41.5%) patients were negative (R0). According to the histopathological examination, median of resected lymph nodes was 46 (range 5-50). Out of all patients, 28 (34.1%) were with

negative lymph nodes for metastasis. In patients with positive lymph nodes, 16 (19.5%) patients had one positive, while 38 (46.3%) patients had two or more positive lymph nodes. LNR=0 has been confirmed in 28 (34.1%) patients, LNR=0-0.2 was in 30 (36.6%), while in 24 patients LNR \geq 0.2 was determined. Adjuvant chemotherapy was administered in 40 patients after surgical treatment. Characteristics of the patients including tumor features, surgical details, resection status, the lymph nodes status and the use of adjuvant chemotherapy are presented in Table 1.

At the time of the study 52 patients (63.4%) were alive, while 30 (36.6%) died. Median survival of all PC patients in our study was 14 months (range 2-69). According to the results of our study, using univariate analysis, factors associated with lower survival in PC were R1 resection margin status and the presence of 2 or more positive lymph nodes (Table 2).

There was no statistically significant difference detected in survival outcome of PC patients with negative lymph nodes compared to patients with positive lymph nodes ($p=0.158$). However our results also showed that in relation to the number of metastatic lymph nodes, PC patients with 0 and 1 positive lymph node had better survival outcome than the group with ≥ 2 ($p=0.007$). Also, statistically significant difference in survival outcome was detected between groups with no metastasis in lymph nodes compared to PC patients with 2 or more positive LN (log rank $p = 0, 02$).

According to the results of our study, PC patients with LNR $<$ 0.2 had better survival outcome compared with the group with LNR \geq 0.2 ($p=0.049$). No significant difference was determined between patients with LNR=0 and patients with LNR=0-0.2 ($p=0.616$), as well as among patients with LNR=0-0.2 and with LNR \geq 0.2 ($p=0.236$).

Multivariate analysis comprising factors that revealed significant associations during univariate testing was conducted and identified presence of 2 or more positive lymph nodes as an independent predictor of survival in PC patients after surgery ($p=0.026$).

DISCUSSION:

Recent studies have shown that the presence of metastases in the lymph nodes can represent a prognostic marker for survival outcome in patients after resection of pancreatic cancer [11,12,13,20]. Our study demonstrated significant difference in survival of PC patients due to the number of positive LN, LNR and resection margin status. However, there was no difference in survival rate of PC patients in relation to the status of LN. Previous investigations have shown that the status of LN has no predictive significance to survival in PC, which was explained by similar survival rate among patients with negative lymph nodes and patients with 1 or 2 positive LN [10,19]. Nevertheless, Riediger H et al thought that these findings are a result of inadequate lymphadenectomy or inadequate histopathological diagnosis [17].

The results of our study showed that patients with negative or 1 positive lymph node, observed together, have a significantly better survival rate than patients with 2 or more positive lymph node. Also, using the univariate analysis we identified presence of 2 or more positive lymph nodes as a factor of lower survival rate in PC patients after surgical treatment. Results of Murakami et al. and House et al. studies showed similar results [14,20]. In our study when patients with 0 and 1 positive lymph node are considered separately, no difference in survival of these two groups of patients was registered, which is consistent with the findings of Murakami et al [20].

LNR value presents a ratio of positive and total number of evaluated lymph nodes, indicating the number of metastatic lymph nodes and resection volume of lymph nodes. Earlier

studies have shown that the value of LNR above 0.15-0.20 is associated with lower survival [17, 18,20]. The results of our research showed that patients with LNR \geq 0.2 have lower survival rate. Pawlik and colleagues have identified LNR as a significant prognostic factor for survival, indicating that the risk of death increases with higher values of LNR [11]. In this study, LNR was observed as an independent predictor of survival outcome. However, Murakami and al have not highlighted LNR as the predictive factor for survival in PC patients. [20]

Results of our study showed that selected R1 resection margin status and the presence of 2 or more positive lymph nodes are factors significantly associated with poorer outcome which is in line with other conducted studies [15-17,20].

According to results of our study, we can conclude that number of positive LN presents more significant prognostic factor than LNR in patients with PC after surgical therapy.

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