Journal of Surgery
[Jurnalul de Chirurgie]
Research Article Open Access

Ki 67 as Prognostic Factor in Surgically Resected Pancreatic Ductal Adenocarcinoma

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Abstract

Background: Pancreatic ductal adenocarcinoma is one of the most aggressive neoplasms, with a poor prognostic and overall survival, most of the patients (over 80%) being diagnosed in advanced stages of the disease, either with distant metastasis or with the locally unresectable tumor. The Ki-67 antigen is a nuclear antigen expressed in all cellular phases (except for the G0 phase) and a high Ki-67 index can be correlated with a recurrence rate of tumor and survival.

Aim: The aim of our study was to demonstrate if the Ki-67 index can be used as a negative prognostic factor for survival.

Methods: We reviewed retrospectively all patients with pancreatic ductal adenocarcinoma (confirmed histologically) and were selected only those with resectable tumors (19.5%). For these patients, immunoreactivity for Ki-67 was evaluated according to the percentage of positive tumor nuclei. The survival was calculated from the data of surgery to a patient's death.

Results: 19.5% of patients were diagnosed with surgically resectable tumors, with a mean tumor's size of 3.3 cm. The overall survival rate at 2 years was 21.15%. The patients with a Ki-67 index over 80% had a significantly lower average survival than the other patients.

Conclusions: The immunohistochemistry staining for Ki-67 can be applied as a prognostic marker for survival in resectable ductal pancreatic adenocarcinoma.

Keywords: Ki-67; Pancreatic ductal adenocarcinoma; Prognostic factors; Survival

Introduction

Pancreatic Ductal Adenocarcinoma (PDAC) is the most common malignant tumor of the pancreas (over 90%) [1,2] and one of the most aggressive neoplasms, with a survival of 2 years of 20% and 5 years of 5% [3]. Over 75% to 80% of patients with PDAC are diagnosed in advanced disease stages, either with distant metastasis or with the locally unresectable disease [4-6] and over 62% of patients with resectable tumors will develop liver metastasis after curative surgery [7]. The average survival in patients with surgical treatment is approximately 17-21 months, but this may be improved if patients follow adjuvant chemotherapy [8-12]. Tumor size, lymph nodal metastasis, perineural and microvascular invasion are considered as prognostic factors for pancreatic ductal adenocarcinoma [3,13].

The Ki-67 antigen, cell cycle and cell proliferation marker is a nuclear antigen expressed in all cellular phases, except for the G0 phase [14]. Height Ki-67 index can be correlated with a recurrence rate of tumor and survival [15].

Materials and Method

We reviewed retrospectively all patients admitted to a single university center between 1 January 2008 and 31 December 2016 and who were diagnosed with pancreatic cancer (ICD C25.0, C25.1, C25.2, C25.3, C25.4, C25.7, C25.8, and C25.9). Of these patients, only those with surgically resected pancreatic ductal adenocarcinoma were included in the study. For those patients who met the criteria for inclusion in the study, the observation sheets, postoperative evolution, tumor size, the final histopathological tumor staging, and survival rate were analyzed. The survival was calculated from the date of surgery to the patient's death (the date of death was provided from the population record database).

For every case, was selected one paraffin block of primary tumor for the immunohistochemical detection of Ki-67. Immunoreactivity for Ki-67 was evaluated according to the percentage of positive tumor nuclei.

The data obtained were processed using IBM SPSS Statistics for Windows, and the Mann-Whitney-U test, ANOVA, independent T-test were used to compare the means and the differences between two independent groups on the same continuous, dependent variable, and the chi-square test, odds ratio, and Fisher exact test were used to determine the difference between two groups or if there is a relationship between two categorical variables, and Kaplan-Meier method with log-rank and Breslow tests of significance were used for overall survival. The obtained results were considered statistically significant at a $p<0.05$.

Result

In our surgical unit, 349 patients were diagnosed with pancreatic carcinoma during 1 January 2008 and 31 December 2016. Of these, 281 patients (80.5%) were admitted in advanced disease (with metastasis at a distance or at a locally advanced stage) and benefited from biliodigestive anastomosis (n=171), pancreatic biopsies or metastasis biopsies (n=17)

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Received April 09, 2019; **Accepted** April 28, 2019; **Published** May 05, 2019

Citation: Andriesi-Rusu F, Trofin A, Cianga-Spiridon I, Vlad N, Vasilescu A, et al. Ki 67 as Prognostic Factor in Surgically Resected Pancreatic Ductal Adenocarcinoma. Journal of Surgery [Jurnalul de chirurgie]. 2019; 15(1): 25-27

or chemotherapy alone (n=93). Sixty-eight patients (19.5%) were diagnosed with surgical resectable pancreatic tumors, located in the pancreatic head (n=60) or body and tail (n=8).

Of all histologically confirmed pancreatic ductal adenocarcinomas, immunohistochemical stains could be achieved in only 62 patients: 44 with duodenopancreatectomy, 8 splenopancreatectomy, 2 pancreatic biopsies, and 8 metastasis biopsies. The patient's group was composed of 29 women and 33 men, with an average age of 60.73 years.

In our study, we included only the patients with surgically resectable tumors and the patient with biopsies were excluded. The size of tumors located at the pancreatic head ranged from 0.5 cm to 5 cm, averaging 3.06 cm, and those at the body/tail were between 3 cm and 6 cm, averaging 3.9 cm. The mean overall survival for patients with pancreatic head tumors was 15.6 months and those with body/tail pancreatic tumor were 12.3 months. The survival rate at 2 years was 21.15% (25% for pancreas head tumors and 0% for body and tail tumors).

Interpreting the immunohistochemistry slides (Figure 1) and establishing the proliferation index for Ki-67 was performed by a consultant anatomopathologist, and Ki-67 staining was scored by a percentage on a scale of 1-95% positivity.

Depending on the Ki-67 tumor proliferation index, we divided the patients into 3 groups: lot 1 (27 patients) with Ki-67 between 0 and 40%, lot 2 (16 patients) with Ki-67 between 40% and 79% and lot 3 (7 patients) with Ki-67 greater than 80%. There were no differences between the Table I shows that the average survival of group 3 (5,57 month), patients with a Ki-67 tumor proliferation index of over 80% is significantly lower than the patients in the first two groups (14,22 month respectively 13,84 month) with a p statistically significant (p=0.032). Kaplan-Meier curves and the log-rank test demonstrated that the Ki-67 index over 80% was significantly associated with poor survival (p=0.002) (Figure 2).

Discussion

Pancreatic cancer is recognized as one of the most aggressive neoplasms, due to both hypovascularization and the presence of peritumoral fibrous stroma, conditions leading to hypoxia and a low intake of nutrients, creating an environment in which only the most aggressive forms of cancer can develop. These characteristics make pancreatic cancer resistant to chemotherapy [16].

The low survival rate of patients with pancreatic cancer of only 24% in the first year of diagnosis and only 5% at 5 years after diagnosis can be explained by the late diagnosis of this disease due to the lack of specific symptomatology in the early stages. Thus, in about 80% of cases, patients are diagnosed in stage IV of the disease [4-6]. Also, most of the patients we followed-up in our study were diagnosed at an advanced stage and only 19.5% were admitted with surgically resected tumors. Of the patients treated surgically, the mean overall survival was only 15.1 months, and the survival rate at 2 years was only 21%. So it is important to identify prognostic factors in pancreatic cancer to improve treatment strategies.

The purpose of our study was to demonstrate whether the Ki-67 tumor proliferation index can be used as a negative prognostic factor for survival.

Ki-67 is a nuclear proliferation-associated antigen, and it is expressed in the nuclei of cells in the active phases (G1, S, G2, M) of the cell cycle, it can be used to estimate the proportion of active cells over the cell cycle [3,15]. Therefore, Ki-67 as a marker of tumoral proliferation can serve as a prognostic factor for survival.

The role of Ki-67 as a prognostic factor remains uncertain, while some studies have found correlations between increased tumor proliferation index and low survival rate; other studies denied these results [17].

Table I: Survival time vs Ki-67 index.

Means and Medians for Survival Time								
Ki-67 proc3	Mean[a]				Median			
	Estimate	Std. Error	95% Confidence Interval		Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
0-40	14.222	1.585	11.116	17.329	14.000	3.462	7.215	20.785
41-80	13.844	1.791	10.334	17.353	13.000	1.333	10.387	15.613
80-100	5.571	1.720	2.201	8.942	5.500	3.273	0.000	11.916
Overall	12.890	1.134	10.668	15.112	12.000	0.964	10.110	13.890
a Estimation is limited to the largest survival time if it is censored								

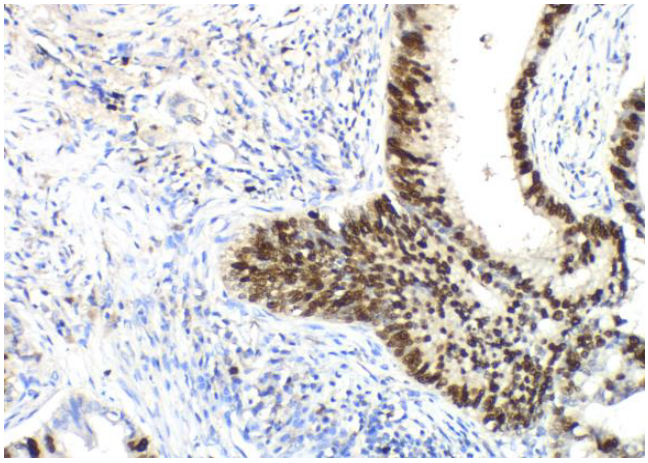

Figure 1: HE-Ki-67 (Ki-67 staining appears as brownish-yellow granules in the nucleus).

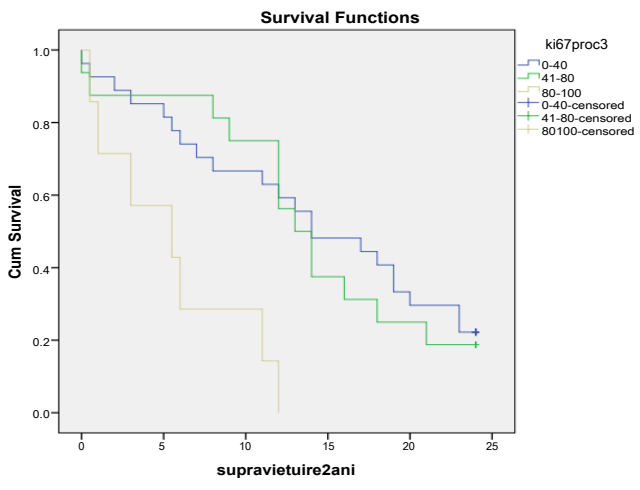

Figure 2: Poor survival rates in patients with elevated Ki-67 index three groups in terms of gender or age distribution, nor in the primary tumor size.

Our study found that the mean survival was approximately 2.5 times lower in patients with a Ki-67 tumor value index greater than 80%, the statistically significant difference. The Kaplan-Meier survival analysis reveals a statistically significant difference in 2-year survival between patients with low and high level (over 80%) of Ki-67 expression (p=0.002).

Conclusion

In conclusion, we can argue that immunohistochemical staining for Ki-67 can be applied as a prognostic marker for survival in resectable ductal pancreatic adenocarcinoma. The Ki-67 index over 80% is associated with poor overall survival.

Conflict of Interest

Authors have no conflict of interest to disclose.

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