

## MOLECULAR FACTORS WITH PREDICTIVE VALUE FOR THE SURVIVAL RATE IN PANCREATIC CANCER: FOCUSING ON CA 19-9

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**Abstract:** The incidence of pancreatic neoplasm has increased exponentially over the last decades in many parts of the world, and moreover it has become the fifth or even sixth cause of death by cancer in the Western countries. Still, little is known about this disease, since the main disadvantage encountered in pancreatic cancer is the fact that the diagnosis is established too late despite the development of new technologies, while also most of the studies carried out have not been able to identify the significant risk factors for pancreatic. In this way, in the present mini-review we want it to make a short description for the main molecular factors with predictive value for the survival rate in pancreatic cancer and by focusing especially on the CA 19-9. Thus, it seems that CA 19-9 should enter in the arsenal of methods for monitoring the condition of the operated patients and also be a tool for the prognostic evaluations. Also, some of the results we describe here are suggesting that tumor-metastatic involvement of LN 8a can be a strong predictive factor of aggressive tumor biology and, therefore, of the early existence of metastatic disease.

Historically speaking, the CA 19-9 was described for the first time by Koprowski et al. and represents an associated tumoral tissue carbohydrate antigen found on the surface of many types of gastrointestinal tumoral cells. In this way, Koprowski immunized colorectal cancer cell lines in mice and then isolated the CA 19-9 monoclonal antibodies from the splenocytes of the respective mice. Moreover, subsequent studies have shown that the antigen is normally present in salivary mucus and pancreatic exocrine juices, so that, although it originates from colorectal tumoral cell lines, is currently useful in the diagnosis, prognosis, evaluation and monitoring of patients with cancer of the pancreas (Berger et al., 2004; Brockhaus et al., 1985).

Also, some researchers have tried to demonstrate the usefulness and efficiency of sequential determination in the dynamics of CA 19-9 in the serum of patients during the postoperative monitoring period. Probably this type of studies was first carried out in 1986 at the National Cancer Institute Bethesda, the authors noticing that patients who experienced a decrease in serum levels to normal values after the operation had a better survival rate than those in which the marker levels maintained at the same increased level. In addition, they have demonstrated that an increase in the levels of CA 19-9 > 95U/mL or four times its lowest value, immediately postoperatory, represents a factor of prediction of the disease progression (Glenn et al., 1988).

Moreover, other authors have shown that elevated serum level in the postoperative period precedes the occurrence of lesions detectable through CT or clinical examination, with 2 up to 9 months (Tian et al., 1992).

Thus, Montgomery et al. has shown that periodic measurements of the CA 19-9 postoperative level is the best predictor for the survival without recurrence period "disease free survival" and also for the total period of survival. He also has shown that patients in which the level of CA 19-9 returns to normal values for 3 to 6 months, have longer periods of overall survival and survival without relapses than those in which the level remains high. Moreover the aforementioned author noticed that the survival rate of the patients in which the postoperative level of CA 19-9 has been less than <180 U/mL at 1 and 3 months, was similar to that of the patients in which the CA 19-9 level returned to normal values in 3 to 6 months (Montgomery et al., 1997).

Also, by assessing the usefulness of CA 19-9 in patients with pancreatic cancer versus those with benign lesions, Safi et al. found in 92% of patients with pancreatic adenocarcinoma a higher than normal level >37 U/ml, for 775 values > 120 U/ml, with a median value of 528 in patients neoplasm. In contrast, they also found values of 18.14 7 U/ml in patients with chronic pancreatitis, acute or concerned with other benign tumors. On another group of patients with different forms of neoplasia (colorectal, gastric, esophageal or extra-digestive) most patients have had CA 19-9 levels within normal limits. In this series, the sensitivity, specificity and accuracy were 92 %, 85% and 82 % (Safi et al., 2006).

In addition, Berger et al. have analyzed retrospectively 129 patients who have had determinations of CA 19-9 before resection between the years 1990 and 2002. They have studied not only the correlation between the level of antigen and recurrence or survival, but also the digestive patients with detectable antigen in serum. The level of the fact that a good preoperative neurological 10-9 has been grouped into 4 categories: undetectable, normal <37, increased 37 to 200, more than increased > 200 U/ml. Moreover, the results were contained from 0 to 16.300 U/mL. In addition, the median overall survival and survival at 5 years were of 19 months and 11 % respectively. Survival was similar between non-secretory and those with normal level, and for both groups the survival was statistically significantly higher than of the other 2 groups with values elevated above normal (p = 0,003). Also, the only significant predictive factor for survival, after the univariate and multivariate analysis was the presence of tumor adenopathies (p = 0.015 and 0.002) and the level

of CA 19-9 ( $p = 0.003$ ). Although the group of patients with normal and undetectable values was submitted with advanced disease, the overall survival was superior (Berger et al., 2004).

Moreover, there are few studies in the literature about CA 19-9 non-secretory patients. In this way, it might be foreseeable that these patients would have a worse prognosis because the level of antigen can not be assessed and, therefore, the prediction for the response to treatment, and for the recurrence and survival is not possible. However, in this study, the non-secretory group had the same prognosis as the one with normal values of the antigen during the preoperative stage. The median survival for these 2 groups of patients was similar, 32, 35 months respectively. Furthermore, these patients presented a significantly better survival than those with higher levels of antigen, in both univariate and multivariate statistical analysis. In fact, the patients with undetectable level of antigen had a much higher median value of recurrence-free survival than the other groups: 27 vs. 14, 10 and 10 months respectively, despite the fact that it did not present a clear statistical significance.

The second positive predictive factor resulted through uni- and multivariate analysis was the presence of tumoral adenopathies, a fact found in other studies as well. Still, it is difficult and early to draw definitive conclusions because the groups of patients are not numerically statistically sufficient. Also it remains unclear why the CA 19-9 non-secretory patients have better prognosis even if the tumor adenopathies are present. For this reason, the authors consider that for resected patients in which the CA 19-9 preoperative level of is undetectable, the aggressive surgery/therapy must and it is worth being performed (Berger et al., 2004).

To determine if the level of CA 19-9 can be predictive for the tumor status and survival and if a change in the postoperative level towards the preoperative level may represent another prognostic factor for survival, Ferrone et al. group also analyzed the parameters on a group of 424 patients with pancreatic ductal adenocarcinoma undergoing pancreatic resections, during the period January 1985 to January 2004. In 176 of these cases, the CA 19-9 values have been determined in the preoperative stage, and in 111 in both pre- and postoperative. Survival was evaluated from the first CA 19-9 measurements in post operative (median period was of 39 days) until death or the last inspection visit (Ferrone et al., 2006).

In this way, out of 176 patients, 128 (73 %) had T3 lesions, 99 patients (56 %) N1 status, while 138 (78 %) have benefited from duodenopancreatectomy. The median level of preoperative CA 19-9 was lower in patients with N0 status, as compared with N1 patients (9 vs. 164 U/ml, nonparametric  $p = 0.03$ ) and in patients with T1/T2, when compared with the patients with T3 injuries (41 vs 162 U/ml,  $p = 0.03$ ).

Also, the median postoperative monitoring of the 111 patients lasted for 1.8 years (range 1 - 12.9 years) achieving an actuarial survival at 1, 3, and 5 years of 70 %, 36% and 30 % respectively. According to the results of the multivariate analysis, the following parameters were significant predictive factors of survival:

- a decrease in the level of CA 19-9 ( $p = 0.0005$ );
- the absence of tumor adenopathies ( $p = 0.001$ );
- reduced T status ( $p = 0.0008$ );
- the postoperative level of CA 19-9 < 200 U/ml ( $p = 0.0007$ ).

In this way, it seems that that the preoperative level of CA 19-9 correlates with tumor stage in patients with pancreatic ductal adenocarcinoma, while both postoperative decrease in CA 19-9 level and a value less than 200 U/ml are strong survival predictive factors even after the adaptation/adjusting for tumor stage. Thus, CA 19-9 should enter in the arsenal of methods for monitoring the condition of the operated patients and also be a tool for the prognostic evaluations (Ferrone et al., 2006).

As mentioned, despite the fact that CA 19-9 was initially described as a marker in colorectal cancer, further studies have shown that in fact its most important clinical utility is actually in pancreatic cancer (Koprowski et al., 2009; Safi et al., 2006; Ritts et al., 1997). Moreover, the results of several studies define it as the main tumoral marker of pancreatic cancer, with a sensitivity and specificity that have been reported between 68% - 94% and 76% to 100% respectively (Karachristos et al., 2005).

In addition, Cleary et al. have conducted a retrospective study on 123 operated patients between 1 January 1988 and 31 December 1996 and full postoperative monitoring in order to identify the prognostic factors of survival. Average survival was 31.7 +/- 3.5 months, and median survival 13.6 months. They were 18 patients (14.6 %) who survived 5 years, including 5 patients (4.1 %) who survived more than 10 years. The 18 5 years survivors were represented by: 13 patients with Whipple's resection, 4 with distal pancreatectomy and one with total pancreatectomy (Cleary et al., 2004).

Moreover, the univariate analysis revealed that the size of the tumor, jaundice absence on arrival at the physician, the absence of tumor adenopathies, small tumoral grading and small tumoral stage are all significant predictive factors of survival.

On the other hand, only the tumor stage (hazard ratio CI 95% stage IIA 1.5 (0.8 - 2.8), stage IIB 2.6 (1.4 - 4.7), stage III 1.8 (0.8 - 4.3) and tumoral grading (hazard ratio CI 95 %) moderately differentiated 1.6 (0.9 - 2.8), poorly differentiated 3.1 (1.6 - 3.5) were independently associated with survival after applying a multivariate Cox proportional hazards model. In this way, starting from the conclusion that long-term survival is only possible if the disease is identified

in early stages, the authors consider that further research should be made just for the purpose of discovering new screening strategies for early diagnosis of this disease (Cleary et al., 2004).

In addition, other authors, such as Kuhlmann et al., noted with surprise that although many recent studies have shown that microscopic radical resection is the strongest independent predictive factor for long-term survival, the survival rate remains low even after the R0 resection (Wagner et al., 2004; de Castro et al., 2004; Kuhlmann et al., 2004).

Also the Han et al. group after the univariate analysis performed on a group of 242 patients operated between 1985 and 1999 found a median survival of 14.8 months and 5 years survival of 12.1 %. Tumor size, the extent of tumor invasion, the lymph node metastases, the tumoral stage and the margins of resection were identified as significant prognostic factor ( $p < 0.05$ ). On the other side, age, sex, blood transfusions, the ACE level, adjuvant therapy and histological grading were not been associated with favorable prognosis. In the multivariate analysis using Cox proportional hazards model, the tumor size, stage and the resection margins had statistical significance ( $p < 0.05$ ). Also, the lymphatic metastases statistical significance was at the limit ( $p = 0,065$ ) (Han et al., 2006).

In addition, the Sperti research group carried out a retrospective study on 113 patients undergoing curative resection for pancreatic adenocarcinoma between 1970 and 1992. In this way, the postoperative mortality was 15% (5% in the last 11 years) and the actuarial survival at 5 years of 12% being influenced by age ( $p = 0.03$ ), portal resection ( $p = 0.02$ ), resection radicality ( $p = 0.01$ ), the number of transfused blood units ( $p = 0.01$ ), the degree of differentiation of the tumor ( $p = 0.002$ ), the status of the lymph nodes ( $p = 0.7001$ ), the perineural invasion ( $p = 0.01$ ), the tumor size ( $p = 0.008$ ), preoperative pre-existing diabetes mellitus, ( $p = 0.001$ ), as well as the tumoral stage ( $p = 0.0001$ ).

Also, the multivariate analysis indicated that only stage, DM, age and tumoral grading are independent predictive factors for long-term survival. On the contrary, the type of resection (Whipple, subtotal, total or distal) did not affect the prognosis. Moreover, the survival at 5 years during the period 1970 - 1981 was 14 %, and, during 1982 to 1992 11 %, with no statistical difference. These considerations suggest that in fact the patient and tumor characteristics affect the long-term survival and not the surgical process employed (Sperti et al., 1996).

In another very relevant study, Cameron et al. reported a survival at 5 years of 19% with a median value of 11.9 % on a group of 89 patients with cephalic duodenopancreatectomy. In this way, the 81 discharged patients have been monitored and it was statistically proved that the absence of tumor adenopathies of tumor invasion of the vessels have favored the long-term survival. But the strongest predictive factor was the absence of lymph node metastases, these patients having a median survival of 55.8 months, compared to the 11 months of those patients with adenopathies ( $p < 0.05$ ). Blood transfusions were also a predictive factor, the patients receiving two or fewer units of blood having a median survival of 24.7 months, as compared to the 10.2 months for those receiving 3 or more units ( $p < 0.05$ ). Still, the most important factor of prognosis for long-term survival following duodenopancreatectomies for pancreatic cancer is the tumor biology (the status of the lymph nodes and vascular invasion) (Cameron et al., 1991).

Moreover, based on the fact that the process of angiogenesis is required for the tumor development, Khan et al. evaluated the prognostic value of intratumoral microvascular density (MVD) on pieces of resection for pancreatic ductal adenocarcinoma and other periampullary cancers. The data from 47 patients (23 with pancreatic cancer and 24 with periampullary tumors, with an average age of 62.0 years) who survived the curative resections R0/R1 were analyzed. In this way, the sections of the resection were stained by immunohistochemistry for CD-34 and the MVD was determined (magnification  $\times 200$ ). This parameter was correlated with the histopathological data and survival determined through Cox multivariate analysis. The average survival for the sub-group with pancreatic cancer was 18.4 months ( $SE = 2.7$ ), while for other periampullary tumors sub-group it was significantly higher (81.2 months,  $SE = 9.9$ ). Also, for the patients with pancreatic cancer MVD is a significant predictive factor of survival after the multivariate analysis ( $p = 0,002$ , HR 13.60), together with the microscopic tumor involved resection edges ( $p = 0.003$ , HR = 15.18). Moreover, MVD in pancreatic cancer correlates with survival (Khan et al., 2002).

In addition, the Fogar group has tried to find a correlation between the immunophenotyping of blood lymphocytes of patients with pancreatic cancer and the tumoral stage, grading and survival, being well-known the fact that affected immunity in the infaust prognosis of patients with pancreatic cancer. In fact, the authors studied extensively with the following subsets: 115 patients with pancreatic cancer, 44 with chronic pancreatitis, 23 with tumors of the biliary ducts and 34 healthy subjects. The survival-related information was accessible only in 77 patients with pancreatic cancer. Moreover, the subsets of lymphocytes were determined by fluorescent activated cell sorting method (fluorescent activated cell sorter - FACS) (Fogar et al., 2006).

Also, in the patients with pancreatic cancer, the total number of lymphocytes was lower than in the patients with chronic pancreatitis and in healthy subjects, while the subset of CD8+ lymphocytes was higher than in healthy subjects. Moreover, in the advanced stages of pancreatic cancer (IIB - IV;  $2 = 11.55$ ,  $p < 0.05$ ) (Magistrelli et al., 2000) the number of circulating lymphocytes was lower than in the early stages 0 and IIA. Also by Cox regression method both the tumoral stage ( $p < 0.001$ ) and total number of lymphocytes ( $p < 0.05$ ) were identified as significant prediction factors. The reduction of the total number of lymphocytes from circulation is the main immunological change that occurs in advanced pancreatic cancer. In this way, it seems that the survival of these patients depends mainly on the tumoral stage

but is also influenced by the number of circulating lymphocytes, suggesting that immune system plays an important role in the changes caused by tumor development (Fogar et al., 2006).

In fact, Kawarada et al. assessed the impact of metastatic spread of tumor cells in 8a and 16b1 lymph nodes (after the Japanese classification - Japanese Pancreas Society) upon survival in patients with periampullary neoplasia. As a matter of fact, it is well known that lymphatic drainage in cancer of the pancreas has been extensively studied in Japan which brought about a new classification (JPS) (Kawarada et al., 2003).

Moreover, in another Japanese study by Kayahara et al. the metastases developed in the lymph nodes surrounding the common hepatic artery (JPS-LN 8a) and in the retroperitoneal lymph nodes posterior of the head of the pancreas (JPS-LN 16b1) appeared in a proportion of 9.7% and 12.9%, respectively. There was also a significant correlation between tumoral invasion of the anterior duodenal pancreatic lymph nodes (JPS-17 LN) and the invasion in LN 8a as a significant association between the LN16b1 involvement and both the posterior lymph node groups (JPS-LN13) as well as the one around AMS (JPS-LN14). In this way, the main results were: 13 out of 54 and 10 out of 44 assessable patients had metastasis in the LN 8a and respectively 16b1 lymph nodes (Kayahara et al., 2002).

Also, the metastasis in the 8a group was associated with a significant reduction in median survival (197 vs. 470 days;  $p = 0,003$ ), while the metastasis in 16b1 group did not affect survival (457 vs. 503 days;  $p = 0,185$ ). Also, the multivariate analysis showed that the 8a lymph node status has the highest prediction of survival ( $p = 0,006$ ). The median survival of patients with metastasis in the 8a ganglion was not significantly different from that of 81 patients with lymphatic metastasis at the time of diagnosis of periampullary tumor. (98 days;  $p = 0,072$ ). Also, the 8a ganglion represents an independent prognostic factor in periampullary malignancies while 16b1 ganglion is not. In this way, the survival of patients with positive LN8a was not significantly different from that of patients with metastatic disease present at the time of diagnosis. Thus, the preoperative determination of 8a ganglion status may have particular significance in selecting patients for treatment.

These results are clearly suggesting that tumor-metastatic involvement of LN 8a can be a strong predictive factor of aggressive tumor biology and, therefore, of the early existence of occult metastatic disease. Also, it seems that positive LN 8a patients would benefit from treatment with a palliative intent rather than surgery. If these results are to be confirmed by other prospective studies, performing routine diagnostic laparoscopy with LN8a node sampling could change the management for approximately 20% of the patients. Still, although the laparoscopic biopsy of regional lymph nodes has been described, is not carried out routinely (Conlon et al., 2006).

In addition, the ganglionic laparoscopic biopsy has a number of advantages over conventional sampling through laparotomy at the moment of resection. LN8a is laparoscopic accessible but it also important to mention that special caution should be taken because of its vasculature from major vessels, with the origins in the AHC (common hepatic artery) and venous drainage into veins tributary to the portal vein (Connor et al., 2004).

Also, the Sohn et al. group has studied the role of potentially predictive factors on a group of 616 patients operated for pancreatic tumors between January 1984 and July 1999. In this way, out of these, 526 (85%) have benefited from duodenopancreatectomy for locations on the head, neck and uncinate process of the pancreas, 52 (9%) from distal pancreatectomy for tumors located in the body or tail (of the pancreas) and 38 (6%) from total pancreatectomy for adenocarcinoma expanded throughout the gland. Moreover, perioperative mortality was 2.3%, and the incidence of postoperative complications of 30%. The median postoperative hospitalization was 11 days. The average tumor diameter was 3.2 cm, with 72% of the patients having tumor adenopathies, 30% edges of positive tumor resection and 36% poorly differentiated neoplasm. Tumors located in the body - tail were bigger (4.7 vs 3.1 cm,  $p < 0,0001$ ), had a lower rate regarding the presence of tumor adenopathies and less poorly differentiated tumors (29% vs 36%,  $p < 0,001$ ), when compared with the tumors located on the pancreatic right-hand side. Also, overall survival for the entire cohort was 63% to 1 year, 17% to 5 years, with a median value of 17 months. For the right side pancreatic lesions the survival at 1 and 5 years was 64% and 17% respectively, when compared to 50% and 15% for pancreatic lesions on the left side (Sohn et al., 2000).

In addition, the factors which were found to have a significant independent prognostic after applying multivariate analysis were: the negative resection margins (HR= 0.64, CI= 0.5-0.82,  $p = 0,0004$ ); the tumor diameter < 3 cm (HR= 0.72, CI= 0,57 - 0,90,  $p = 0,004$ ); the estimated blood loss < 750 ml (HR= 0.75, CI= 0.58 to 0.96,  $p = 0,02$ ); a good/moderate tumor differentiation (HR= 0.71, CI= 0,56-0,90,  $p = 0,005$ ); postoperative chemotherapy (HR= 0.50, CI= 0,39 - 0.64,  $p < 0,0001$ ), as well as tumor location in the head, neck, or uncinate process gained statistical significance following the multivariate analysis (HR= 0.60 CI= 0.35-1.0,  $p = 0,06$ ). Also, we have to mention that so far the pancreatic resection remains the only hope for a prolonged survival of the patients with pancreatic adenocarcinoma. Moreover, oncologic resection and tumor characteristics, including the size of the tumor and the degree of differentiation are independent predicting factors. In addition, adjuvant chemotherapy is a strong predictor of survival and almost diminishes from the independent significance of tumor location and lymph status (Sohn et al., 2000).

In this way, Magistrelli et al. have examined the impact of demographic factors, intraoperative and histopathological on survival. Thus, in a retrospective study including 73 operated patients during the period 1988-1998, they reported the absence of operator mortality and a morbidity of 37%. Also, survival at 3 and 5 years was 27% and

13% and disease specific survival at 3 and 5 years of 31% and 21% with a median survival of 16 months. According to the univariate analysis, T and N of the TNM classification have significantly affected the survival ( $p= 0.0017$  and  $0.04$ ) (Magistrelli et al., 2000).

Very relevant in this way is also the study performed by Richter et al., which have studied the long-term results and predicting factors using the uni-and multivariate analysis on a series of 194 patients who were operated by Kausch-Whipple technique. They have obtained a mortality rate of 3.09% and a morbidity of 29.9%. By the multivariate analysis, only curative R0 resection was significantly correlated with a favorable prognosis ( $p < 0.0001$ ). Moreover, for a curative resection, the tumoral adenopathies presence has a prognostic significance in the multivariate analysis. The cumulative survival at 5 years was 25.4%, at 7-years of 12.3% and at 10-years of 8.2% for the patients with R0 curative resection for cephalic adenocarcinoma of the pancreas (Richter et al., 2007).

Also, Sener et al. have retrospectively analyzed 100.313 patients using the national cancer data base in the USA and identified that for all the patients, the significant determinant factors of survival were in the following order: the tumoral stage, the type of treatment and the grading. Moreover, for resected patients, the stage of disease was more significant than the tumor grading (Sener et al., 1999).

In another study, Phoa et al. correlated the preoperative CT with survival, trying to find a prognostic value of it. On a group of 71 consecutive patients with potentially resectable cephalic pancreatic neoplasm the prognostic factors for the CT examination were: the size of the tumor, peripancreatic tissue infiltration, the degree of vascular invasion and factors which determining local nonresectability. Actually, in this study, only 41 of the 71 tumors were resectable, and out of these only 24 radically. The sensitivity, specificity and value of CT positive prediction for assessing nonresectability were 0.67, 0.633 and 0.57 respectively. For a non-radical resection, these values were 0.62, 0.75 and 0.83 respectively. Also, the median survival was 21 months for resectable tumors and 9.7 months for the unresectable ones. Moreover, the resectable tumors having as signs of local nonresectability a tumoral diameter  $> 3$  cm and local unresectability CT signs had short survival, while the median survival of tumors smaller then 2cm was 30 months. Also, the CT signs of local unresectability and the tumor diameter bigger 3 cm seem to have predictive value for low survival after resection (Phoa et al., 2005).

### Conclusions

Thus, it seems that that the preoperative level of CA 19-9 correlates with tumor stage in patients with pancreatic cancer, while both postoperative decrease in CA 19-9 level are important survival predictive factors even after the adaptation/adjusting for tumor stage. In this way, CA 19-9 could enter in the arsenal of methods for monitoring the condition of the operated patients and also be a tool for the prognostic evaluations. Also, some of the results we describe here are suggesting that tumor-metastatic involvement of LN 8a can be a strong predictive factor of aggressive tumor biology and, therefore, of the early existence of metastatic disease.

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