



Editorial

Role of Neoplastic Markers in Pancreatic Adenocarcinoma

Alessandro Coppola ¹, Tommaso Farolfi ^{2,3}, Vincenzo La Vaccara ^{3,*}, Roberto Cammarata ² and Damiano Caputo ^{2,3}

¹ Department of Surgery, Sapienza Università di Roma, 00185 Rome, Italy

² General Surgery, Università Campus Bio-Medico di Roma, 00128 Rome, Italy

³ General Surgery, Fondazione Policlinico Universitario Campus Bio-Medico, 00128 Rome, Italy

* Correspondence: v.lavaccara@policlinicocampus.it

Pancreatic ductal adenocarcinoma (PDAC) is considered one of the “Big Five” lethal cancers, which include lung, bowel, breast and prostate cancer. PDAC is set to be a second-place candidate for the most cancer-related deaths [1].

The poor survival rates in PDAC patients can be explained both by the aggressive behaviour of the disease and by the lack of reliable tools for its early diagnosis.

In 80–85% of cases, PDAC is diagnosed in the advanced or metastatic stages, and only a minority of patients are eligible for radical surgery, which still represents the gold standard treatment [2].

As recently reported by Klaiber et al., early diagnosis would allow doctors to identify PDAC at an early stage, increasing the 5-year survival rate [3].

Following the guidelines of the Food and Drug Administration, despite its low specificity (82%) and sensitivity (79%), CA 19.9 is the only available neoplastic marker recognized for the clinical management of PDAC [4].

Unfortunately, CA 19.9 is not without limitations: first, about 10% of the population does not secrete CA 19.9, causing a large number of false-negatives results; second, cholestatic jaundice could increase CA 19.9 values and may also occur in cases of non-malignant lesions [5].

An aberrant pathway of disialyl Lewis (a) production is responsible for the formation of CA 19.9 (a sialyl Lewis (a) antigen).

The role of this molecule is to maintain immunological homeostasis, and it functions as a ligand for E-selectin on endothelial cells; this explains why PDAC secreting CA 19.9 usually shows biological aggressiveness and why non-secretor PDAC patients have better prognoses [6–8].

For early diagnosis of PDAC, due to the weak and limited evidence reported in the literature, the role of CA 19.9 is still not defined or recognized in clinical practice [9].

Today, a well-established field of clinical application for CA 19.9 is the monitoring of radio- and chemotherapy efficacy in patients with advanced PDAC [10].

As demonstrated by Robert et al. in a retrospective analysis of 342 patients with metastatic PDAC treated with FOLFIRINOX, a CA19.9 decrease after therapy of more than 20% is a prognostic factor for both overall survival (OS) and progression-free survival [11].

In resectable-PDAC patients undergoing surgery, CA 19.9 has similarly been shown to be useful in monitoring during adjuvant treatment to predict disease recurrence [12].

As previously reported, preoperative serum levels of CA 19.9 have limited utility in the diagnosis of PDAC, but in recent years, this marker has become increasingly important in determining the prognosis and being part of the decisional therapeutic process of this malignancy [13].

More in detail, Ferrone et al., in 2006, demonstrated that a pre-operative cut-off value of CA 19.9 under or above 1000 U/mL reflected a statistically significant longer median OS when the two groups were compared, with survival changing from 28 months to 12 months [14].



Citation: Coppola, A.; Farolfi, T.; La Vaccara, V.; Cammarata, R.; Caputo, D. Role of Neoplastic Markers in Pancreatic Adenocarcinoma. *J. Clin. Med.* **2022**, *11*, 6509. <https://doi.org/10.3390/jcm11216509>

Received: 28 October 2022

Accepted: 1 November 2022

Published: 2 November 2022

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Copyright: © 2022 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

In 2019, a multicenter Italian Study showed that preoperative CA 19.9 serum levels of 100 U/mL or above were associated with worse survival outcomes. They also showed a significant association between CA 19.9 and pathological nodal involvement [15].

Similarly, the ability of CA 19.9 values to predict early local recurrence is also demonstrated by numerous studies. Fiore et al., using a cohort of 120 PADC patients, analyzed the pre-operative CA 19.9 value in combination with the PET/CT maximum SUV level.

Notably, in this report, CA 19.9 values were also significantly associated with oncological outcomes such as early local recurrence and overall survival. In detail, a CA 19.9 value above 698 U/mL in pre-operative measurement is associated with a six-times higher risk of early recurrence [16].

In the past year, the role of pre-operative CA 19.9 in predicting lymph-node positivity (N+) after resection has been explored extensively; in a large series of patients, the Heidelberg group demonstrated that the presence of positive lymph nodes represents one of the most significant prognostic factors for long-term oncological outcomes after upfront surgery in patients with PDAC [17].

CA 19.9 has been used in combination with radiological findings (CT or PET-CT) to improve their sensitivity and specificity in predicting N+ [18,19].

In 2021, Coppola et al. confirmed Mattiucci's findings in a single-center retrospective analysis whereby a cohort of 165 patients with resectable PDAC underwent pancreatic surgery. In this paper, values of CA 19.9 > 37 U/mL were able to predict the presence of positive lymph nodes in the final pathology report. Notably, in the presence of hypoalbuminemia, CA 19.9 was not able to predict lymph nodal involvement [20].

Takahashi et al. confirmed the previous findings in a larger retrospective study. From an analysis of more than four hundred patients with resectable disease, they demonstrated that the overall survival of patients with pre-operative CA 19.9 values greater than 120 U/mL is similar to that of patients with anatomical borderline resectable PDAC. In addition, a reduction in marker levels after neoadjuvant therapies was demonstrated to be a predictor of improved oncological and survival outcomes [21].

Therefore, considering the above-mentioned studies, new perspectives on the role of CA 19.9 must be explored. This marker is becoming crucial in PDAC preoperative staging. As such, the idea of biological resectability in pancreatic cancers where CA 19.9 may represent a fundamental, feasible and inexpensive tool to establish more appropriate therapeutic strategies is gaining momentum; this is particularly true considering the encouraging results of Japanese trials comparing oncological outcomes after neoadjuvant treatments in borderline and resectable patients with PDAC [22].

The second most common neoplastic marker adopted in clinical practice is the serum carcinoembryonic antigen (CEA); its levels have increased by between 30% and 60% in pancreatic cancer [23].

This glycoprotein was detected for the first time in patient with bowel adenocarcinoma [24].

CEA has been proposed as an alternative marker to use in CA 19.9 non-secreting patients; however, the relationship between CEA and PDAC still remains unclear.

In 2016, Imaoka and colleagues published a retrospective study in a series of 433 patients, demonstrating that in patients with metastatic disease, CEA levels represent a survival prognostic factor. In detail, 6.8-month OS was observed in patients with CEA > 5 ng/mL, unlike the 10.3 months in patients with CEA under the previous cut-off [25].

Considering the limited use of CEA alone, many authors have proposed the use of this serum marker in combination with CA 19.9 and other markers to improve its diagnostic power.

In 2008, the Hellenic Group of Oncology found, using multivariate analysis, that higher levels of neoplastic marker, CEA and CA19.9 had a negative impact on the prognosis and survival of patients with unresectable and metastatic pancreatic cancer [26].

More recently, an Austrian study found that the prognostic efficacy of the combination of CEA and CA19.9 was significantly higher compared with single tumor markers [27].

In 2015, Liang et al. investigated the prognostic role of a panel of three markers: CA 19.9, CEA and CA 125.

A series of over 1000 patients underwent pancreatectomy at two independent high-volume institutions, and it was found that the association between CA 19.9, CEA and CA 125 was able to predict poor surgical outcomes with the lowest median survival (5.1 months vs. 23.0 months in the control group). In addition, the authors suggest the possibility of a higher prevalence of early distant metastasis after radical surgical treatments in patients with pre-operative elevated neoplastic markers [28].

Other serum markers such as CA 50 and CA 125 have been widely used, alone and in combination with each other, in order to find a useful tool both for diagnostics and prognostics in PDAC patients with poor results.

In conclusion, the above-mentioned markers seem to be a useful tool in the diagnosis of PDAC, as well as in evaluating its response to neoadjuvant or adjuvant treatment, disease progression and further prognosis.

Unfortunately, there is still not enough evidence to guide decision-making for the treatment of patients with adenocarcinoma of the pancreas.

Future studies with larger cohorts of patients and, ideally, in prospective randomized settings could improve our knowledge on the efficacy of these neoplastic markers, alone or in combination with new technologies such as nanoparticles and/or circulating tumor cells.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflict of interest.

References

- Rahib, L.; Smith, B.D.; Aizenberg, R.; Rosenzweig, A.B.; Fleshman, J.M.; Matrisian, L.M. Projecting cancer incidence and deaths to 2030: The unexpected burden of thyroid, liver, and pancreas cancers in the United States. *Cancer Res.* **2014**, *74*, 2913–2921; Erratum in *Cancer Res.* **2014**, *74*, 4006. [[CrossRef](#)] [[PubMed](#)]
- Zhang, L.; Sanagapalli, S.; Stoita, A. Challenges in diagnosis of pancreatic cancer. *World J. Gastroenterol.* **2018**, *24*, 2047–2060. [[CrossRef](#)] [[PubMed](#)]
- Klaiber, U.; Leonhardt, C.-S.; Strobel, O.; Tjaden, C.; Hackert, T.; Neoptolemos, J.P. Neoadjuvant and adjuvant chemotherapy in pancreatic cancer. *Langenbeck's Arch. Surg.* **2018**, *403*, 917–932. [[CrossRef](#)] [[PubMed](#)]
- Ferri, M.J.; Saez, M.; Figueras, J.; Fort, E.; Sabat, M.; López-Ben, S.; de Llorens, R.; Aleixandre, R.N.; Peracaula, R. Improved Pancreatic Adenocarcinoma Diagnosis in Jaundiced and Non-Jaundiced Pancreatic Adenocarcinoma Patients through the Combination of Routine Clinical Markers Associated to Pancreatic Adenocarcinoma Pathophysiology. *PLoS ONE* **2016**, *11*, e0147214. [[CrossRef](#)] [[PubMed](#)]
- Tsen, A.; Barbara, M.; Rosenkranz, L. Dilemma of elevated CA 19-9 in biliary pathology. *Pancreatology* **2018**, *18*, 862–867. [[CrossRef](#)] [[PubMed](#)]
- Tempero, M.A.; Malafa, M.P.; Al-Hawary, M.; Asbun, H.; Bain, A.; Behrman, S.W.; Benson, A.B., III; Binder, E.; Cardin, D.B.; Cha, C.; et al. Pancreatic Adenocarcinoma, Version 2.2017, NCCN Clinical Practice Guidelines in Oncology. *J. Natl. Compr. Cancer Netw.* **2017**, *15*, 1028–1061. [[CrossRef](#)]
- Miyazaki, K.; Ohmori, K.; Izawa, M.; Koike, T.; Kumamoto, K.; Furukawa, K.; Ando, T.; Kiso, M.; Yamaji, T.; Hashimoto, Y.; et al. Loss of Disialyl Lewis X, the Ligand for Lymphocyte Inhibitory Receptor Sialic Acid-Binding Immunoglobulin-Like Lectin-7 (Siglec-7) Associated with Increased Sialyl Lewis X Expression on Human Colon Cancers. *Cancer Res.* **2004**, *64*, 4498–4505. [[CrossRef](#)]
- Berger, A.C.; Meszoely, I.M.; Ross, E.A.; Watson, J.C.; Hoffman, J.P. Undetectable Preoperative Levels of Serum CA 19-9 Correlate with Improved Survival for Patients with Resectable Pancreatic Adenocarcinoma. *Ann. Surg. Oncol.* **2004**, *11*, 644–649. [[CrossRef](#)]
- Takaori, K.; Bassi, C.; Biankin, A.; Brunner, T.B.; Cataldo, I.; Campbell, F.; Cunningham, D.; Falconi, M.; Frampton, A.E.; Furuse, J.; et al. IAP/EPC study group on the clinical managements of pancreatic cancer. International Association of Pancreatology (IAP)/European Pancreatic Club (EPC) consensus review of guidelines for the treatment of pancreatic cancer. *Pancreatology* **2016**, *16*, 14–27. [[CrossRef](#)]
- Laurent, L.; Sefrioui, D.; Bignon, A.-L.; Parzy, A.; Sidali, S.; Hassine, M.; Gangloff, A.; Galais, M.-P.; Bouhier-Leporrier, K.; Michel, P.; et al. CA19.9 decrease >15% is a predictor of favourable outcome in patients treated for advanced pancreatic carcinoma: Analysis of two independent cohorts. *HPB* **2018**, *21*, 582–588. [[CrossRef](#)]
- Robert, M.; Jarlier, M.; Gourgou, S.; Desseigne, F.; Ychou, M.; Bouché, O.; Juzyna, B.; Conroy, T.; Bennouna, J. Retrospective Analysis of CA19-9 Decrease in Patients with Metastatic Pancreatic Carcinoma Treated with FOLFIRINOX or Gemcitabine in a Randomized Phase III Study (ACCORD11/PRODIGE4). *Oncology* **2017**, *93*, 367–376. [[CrossRef](#)] [[PubMed](#)]

12. Azizian, A.; Rühlmann, F.; Krause, T.; Bernhardt, M.; Jo, P.; König, A.; Kleiß, M.; Leha, A.; Ghadimi, M.; Gaedcke, J. CA19-9 for detecting recurrence of pancreatic cancer. *Sci. Rep.* **2020**, *10*, 1332. [[CrossRef](#)] [[PubMed](#)]
13. Coppola, A.; La Vaccara, V.; Farolfi, T.; Fiore, M.; Cammarata, R.; Ramella, S.; Coppola, R.; Caputo, D. Role of CA 19.9 in the Management of Resectable Pancreatic Cancer: State of the Art and Future Perspectives. *Biomedicines* **2022**, *10*, 2091. [[CrossRef](#)] [[PubMed](#)]
14. Ferrone, C.R.; Finkelstein, D.M.; Thayer, S.P.; Muzikansky, A.; Fernandez-del Castillo, C.; Warshaw, A.L. Perioperative CA19-9 Levels Can Predict Stage and Survival in Patients with Resectable Pancreatic Adenocarcinoma. *J. Clin. Oncol.* **2006**, *24*, 2897–2902. [[CrossRef](#)]
15. Mattiucci, G.C.; Morganti, A.G.; Cellini, F.; Buwenge, M.; Casadei, R.; Farioli, A.; Alfieri, S.; Arcelli, A.; Bertini, F.; Calvo, F.A.; et al. Prognostic Impact of Presurgical CA19-9 Level in Pancreatic Adenocarcinoma: A Pooled Analysis. *Transl. Oncol.* **2018**, *12*, 1–7. [[CrossRef](#)]
16. Fiore, M.; Taralli, S.; Trecca, P.; Scolozzi, V.; Marinelli, L.; Triumbari, E.K.A.; Caputo, D.; Angeletti, S.; Ciccozzi, M.; Coppola, A.; et al. A Bio-Imaging Signature as a Predictor of Clinical Outcomes in Locally Advanced Pancreatic Cancer. *Cancers* **2020**, *12*, 2016. [[CrossRef](#)]
17. Bergquist, J.R.; Puig, C.A.; Shubert, C.; Groeschl, R.T.; Habermann, E.; Kendrick, M.L.; Nagorney, D.M.; Smoot, R.L.; Farnell, M.B.; Truty, M.J. Carbohydrate Antigen 19-9 Elevation in Anatomically Resectable, Early Stage Pancreatic Cancer Is Independently Associated with Decreased Overall Survival and an Indication for Neoadjuvant Therapy: A National Cancer Database Study. *J. Am. Coll. Surg.* **2016**, *223*, 52–65. [[CrossRef](#)]
18. Nanashima-Ichiro, A.; Sakamoto, I.; Hayashi, T.; Tobinaga, S.; Araki, M.; Kunizaki, M.; Nonaka, T.; Takeshita, H.; Hidaka, S.; Sawai, T.; et al. Preoperative Diagnosis of Lymph Node Metastasis in Biliary and Pancreatic Carcinomas: Evaluation of the Combination of Multi-detector CT and Serum CA19-9 Level. *Am. J. Dig. Dis.* **2010**, *55*, 3617–3626. [[CrossRef](#)]
19. Wang, S.; Shi, H.; Yang, F.; Teng, X.; Jiang, B. The value of 18F-FDG PET/CT and carbohydrate antigen 19-9 in predicting lymph node micrometastases of pancreatic cancer. *Abdom. Radiol.* **2019**, *44*, 4057–4062. [[CrossRef](#)]
20. Coppola, A.; La Vaccara, V.; Fiore, M.; Farolfi, T.; Ramella, S.; Angeletti, S.; Coppola, R.; Caputo, D. CA19.9 Serum Level Predicts Lymph-Nodes Status in Resectable Pancreatic Ductal Adenocarcinoma: A Retrospective Single-Center Analysis. *Front. Oncol.* **2021**, *11*, 690580. [[CrossRef](#)]
21. Takahashi, H.; Yamada, D.; Asukai, K.; Wada, H.; Hasegawa, S.; Hara, H.; Shinno, N.; Ushigome, H.; Haraguchi, N.; Sugimura, K.; et al. Clinical implications of the serum CA19-9 level in “biological borderline resectability” and “biological downstaging” in the setting of preoperative chemoradiation therapy for pancreatic cancer. *Pancreatol.* **2020**, *20*, 919–928. [[CrossRef](#)] [[PubMed](#)]
22. Motoi, F.; Kosuge, T.; Ueno, H.; Yamaue, H.; Satoi, S.; Sho, M.; Honda, G.; Matsumoto, I.; Wada, K.; Furuse, J.; et al. Study Group of Preoperative Therapy for Pancreatic Cancer [Prep] and Japanese Study Group of Adjuvant Therapy for Pan-creatic cancer [JSAP]. Randomized phase II/III trial of neoadjuvant chemotherapy with gemcitabine and d S-1 versus up-front surgery for resectable pancreatic cancer [Prep-02/JSAP05]. *Jpn J. Clin. Oncol.* **2019**, *49*, 190–194. [[PubMed](#)]
23. Nazli, O.; Bozdog, A.D.; Tansug, T.; Kir, R.; Kaymak, E. The diagnostic importance of CEA and CA 19-9 for the early diagnosis of pancreatic carcinoma. *Hepatogastroenterology* **2001**, *47*, 1750–1752.
24. Gold, P.; Freedman, S.O. Specific carcinoembryonic antigens of the human digestive system. *J. Exp. Med.* **1965**, *122*, 467–481. [[CrossRef](#)] [[PubMed](#)]
25. Imaoka, H.; Mizuno, N.; Hara, K.; Hijioka, S.; Tajika, M.; Tanaka, T.; Ishihara, M.; Hirayama, Y.; Hieda, N.; Yoshida, T.; et al. Prognostic impact of carcinoembryonic antigen (CEA) on patients with metastatic pancreatic cancer: A retrospective cohort study. *Pancreatol.* **2016**, *16*, 859–864. [[CrossRef](#)] [[PubMed](#)]
26. Papadoniou, N.; Kosmas, C.; Gennatas, K.; Polyzos, A.; Mouratido, U.D.; Skopelitis, E.; Tzivras, M.; Sougioultzis, S.; Papastratis, G.; Karatzas, G.; et al. Prognostic factors in patients with locally advanced (unresectable) or metastatic pancreatic adenocarcinoma: A retrospective analysis. *Anticancer Res.* **2008**, *28*, 543–549.
27. Reitz, D.; Gerger, A.; Seidel, J.; Kornprat, P.; Samonigg, H.; Stotz, M.; Szkandera, J.; Pichler, M. Combination of tumour markers CEA and CA19-9 improves the prognostic prediction in patients with pancreatic cancer. *J. Clin. Pathol.* **2015**, *68*, 427–433; Erratum in *J. Clin. Pathol.* **2015**, *68*, e2. [[CrossRef](#)] [[PubMed](#)]
28. Gu, Y.L.; Lan, C.; Pei, H.; Yang, S.N.; Liu, Y.F.; Xiao, L.L. Applicative value of serum CA19-9, CEA, CA125 and CA242 in diagnosis and prognosis for patients with pancreatic cancer treated by concurrent chemoradiotherapy. *Asian Pac. J. Cancer Prev.* **2015**, *16*, 6569–6573. [[CrossRef](#)]