Editorial

The run for personalized oncological therapy in pancreatic cancer: are we catching up with other tumors?

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The most common type of pancreatic cancers (PC) originates from the ductal cells of the exocrine gland and belongs to the family of adenocarcinomas of the gastrointestinal tract (1-3). In the United States, PC represents the fourth leading cause of cancer-related deaths with 44,000 new cases per year and a comparable number of deaths (2,4). After diagnosis, only 20–30% of PCs can undergo curative treatments, while the rest receives palliation (5). PC is a common malignancy in many high-income countries where significant efforts have tried to find new ways to improve survival. Despite all the attempts, PC remains difficult to cure because it behaves as a systemic disease even in its early stages. Radical resection is the only potential cure, but it is inadequate in 70–80% of the patients who develop recurrent disease within 5 years. The use of neo and adjuvant chemotherapy with or without radiation therapy has shown to prolong survival. However, multimodality interventions have not been a panacea and we have achieved only very small improvements in survival over the last several decades (6). It is not surprising that we need new ways to approach and treat PC since the current ones are not satisfactory (7).

One of the most recent developments in the field of oncology is the realization that tumors that historically were classified and treated as equal, are indeed diverse and respond to therapies in very different ways. The more we look, the more we appreciate that each tumor is unique and it comes with specific mutations in signaling pathways that make them less, or in some fortunate circumstances more sensitive to chemo-radiation or to molecular-targeted therapies.

For patients with PC, the identification of genetic characteristics or morphologic signatures of neoplastic cells that could predict the risk of developing metastases might change the way we will treat PC. For example, in patients who are less likely to metastasize, locoregional therapies could be used more aggressively to downsize tumors in preparation for surgery or to control tumors that are not resectable but that are only localized in the pancreas. On the contrary, for patients with features suggestive of an increased risk of metastatic disease, a more educated and honest discussion about their prognosis and the benefits of surgical resections might be important to avoid unnecessary surgeries, particularly for high-risk surgical patients.

The delivery of personalized therapies, based on characteristic biomarkers, is already a reality for the treatment of other solid cancers (e.g., breast, colorectal, neuroendocrine, melanoma, prostate, lung and sarcomas) (8). Precise oncological treatments have been proven to be more effective, better tolerated and more cost-efficient. Therefore, they should become a priority also for patients with PC. Unfortunately, this is not always the case because PC is far behind other tumors in regard to personalized oncology. There are several reasons why personalized therapy in PC is not as common as for other malignancies. The most obvious is that, when compared to other types of tumors, we don't have the same knowledge of the key biological markers and gene expressions that are responsible for the response to systemic or locoregional therapies, or what are the key pathways that control the progression of neoplastic cells from invading other organs and become metastatic (9).

This gap is slowly closing as shown in the paper by Cuneo and colleagues (3) published in this issue of "*International Journal of Radiation Oncology • Biology • Physics*". The authors report the results of the largest study performed on the effects of c-MET expression in patients with PC. The investigators performed tissue microarray (TMA) analysis on 102 samples of PCs where cytoplasmic levels of c-MET were measured and scored by an independent pathologist who was blinded to the treatments and clinical outcomes. Tumors were stratified into two groups based on the level of c-MET found in the cells. When compared to patients with low expression of c-MET, individuals with high values were more likely to develop metastases within shorter periods of time (median 8.9 *vs.* 22.0 months; P<0.001). The authors also found that patients with low expression of DPC4, and patients with high nuclear staining for thymidylate synthetases (TS), developed distant recurrent disease much quicker than their counterparts. Interestingly, time to local failure was not dissimilar between high and low-risk groups. Using the combination of c-MET, DPC4 and TS, the authors were able to stratify patients in high and low-risk for metastatic disease and found that almost half of the patients in the high-risk group developed metastases within 3 years, while in the low-risk group, almost half were free from metastases within the same period of time.

c-Met is a tyrosine kinase receptor that regulates several signaling transduction pathways including MAPK/ERK, PI3K/AKT, and FAK (10). In cancer, this confers multiple properties such as resistance to chemotherapy, induction of angiogenesis and promotion of metastases (11), directly through the kinase activity, or indirectly through the scaffolding protein Gab1. Other investigators had already shown that c-MET is overexpressed in PC (12) and that high cytoplasmic levels of c-MET are associated with decreased disease-free survival (13-15). However, what is new in Cuneo's *et al.*'s study is that the distribution of c-MET staining was not influenced by preoperative chemoradiation, and that the use c-MET, in combination with several other proteins such as DPC4 and TS, was helpful in predicting patients with shorter overall survival and progression-free survival.

We applaud the investigators for the quality of their study and for expanding our knowledge on how we could use innovative tests to better predict the outcomes of patients with PC. However, we need to be cognizant that this study has some limitations including the small number of patients and that it has not been externally validated yet. Other shortcomings are that the authors did not report the proportion of patients who had positive resection margins, lymphovascular or perineural tumor invasion and the grade of cellular differentiation of the tumors with high or low levels of c-MET expression. These are important details as it is possible that patients who developed early metastases and who had shorter survival were the ones who had tumors with other well-known pathological features associated with poor prognosis.

Despite these limitations, the paper by Cuneo *et al.* (3) is important for several reasons. First, the investigators have shown that the levels of c-MET seem to be insensitive to preoperative chemoradiation contrary to what was indicated in some previous studies. Second, c-MET appears to be a predictor of patient overall and disease-free survival. Third, c-MET could be used in future trials to adjust for the different intrinsic potential that each PC has for the development of metastatic disease. Fourth, the combination of multiple independent predictors might be more accurate than a single protein when trying to discriminate patients at high risk of metastatic disease.

In the context of personalized oncological therapy for PC, Cuneo *et al.* have given us the opportunity to ask more questions that might become the focus of future research:

(I) Ideally, personalized therapy for PC should be initiated before surgery is performed and offered also to patients who might not be resectable. Can we reproduce the same results reported by Cuneo *et al.* from TMA on tumor samples obtained using fine needle aspiration or core biopsies or from other biological fluids such as pancreatic secretions that can be collected endoscopically?

(II) Is c-MET expression higher in patients with other established pathological predictors of poor outcomes such as lymphovascular or perineural invasion or poorly differentiated PC cells?

(III) Is c-MET expression heterogeneous in different parts of PCs?

(IV) Is c-MET expression in metastatic tumors similar to the expression observed in primary PCs?

(V) Can we use the level of expression of c-MET as a proxy for response to chemo or chemoradiation therapy?

(VI) Why was the rate of locally recurrent disease not correlated with the level of expression of c-MET in PC samples?

The study by Cuneo *et al.* (3) is a step forward in our attempt to better understand PC and the many pathways

that could be targeted to improve patients' survival. It provides further evidence that novel kinase inhibitors might play an important role for the treatment of PC as they have shown to enhance the effects of current chemotherapy medications, reduce the risk of tumor resistance and suppress tumor stem cell signaling.

The run for the cure of PC is probably longer than the run for the cure of other tumors, but each step forward is a step closer to the finish line and should be celebrated.

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