**RESEARCH TOPIC CLI23**

# Personalizing Therapeutic Pathways 2.0: A Prospective, Real-Life Observational Study on the Application of Innovative Biological Profiling Techniques in Surgically Treatable Pancreatic Adenocarcinoma

**Research area**
Surgical Area

**Clinical Unit name**
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**Abstract**

State of the Art

Currently, several therapeutic strategies exist for patients with surgically manageable pancreatic adenocarcinoma. For years, the literature has attempted to determine the optimal approach, especially for resectable pancreatic adenocarcinoma (whether upfront surgery, neoadjuvant chemotherapy, or a combination of both) without reaching a definitive consensus [1-2]. This lack of clarity likely stems from the fact that a "one-size-fits-all" solution does not exist; treatment efficacy depends on multiple variables. The turning point may lie in personalized medicine, which has finally become pragmatically feasible through emerging technologies in various oncological contexts. The evaluation of circulating tumor DNA (ctDNA) has been shown in other oncological contexts to correlate with the presence of micrometastases—currently a primary rationale supporting the use of neoadjuvant therapy in this field [3-6]. The ability to exclude the presence of micrometastatic disease at the time of diagnosis would allow for the identification of patients who might achieve optimal outcomes through upfront surgery, thereby avoiding the delays associated with neoadjuvant regimens (which can extend up to six months). Conversely, the identification of patients whose tumor cells have likely already disseminated to distant organs could prevent highly invasive surgical procedures that may provide no therapeutic benefit in the context of systemic disease. Furthermore, the emergence of different effective chemotherapy regimens and impending novel targeted molecules has complicated the selection of optimal therapies for individual patients. While identifying the tumor's mutational landscape can reveal sensitivity profiles for specific drugs, the proportion of actionable interactions remains limited and unclear, benefiting only a small subset of patients. In this scenario, the development of patient-specific organoids offers the potential to rapidly screen various therapeutic regimens, potentially identifying the most effective treatment for the patient's specific disease before clinical administration [7-10].

Research Design and Methodology

This study will enroll 100 patients with resectable or borderline resectable pancreatic adenocarcinoma. At enrollment, demographic, clinical, and biometric data will be recorded, alongside radiomic profiles and the assessment of ctDNA. Based on these initial findings, with the support of an AI algorithm, patients will undergo either upfront surgery or neoadjuvant chemotherapy following common and good clinical practice after a multidisciplinary meeting. Once sufficient biological material is obtained, in the upfront group, a patient-specific organoid cohort will be developed for each participant. These unique organoids will be used to test various chemotherapeutic regimens and molecular compounds, including the one indicated by the referring oncologists in the, multidisciplinary setting , prior to clinical administration. In this way, we aim to evaluate the ability of this process to identify the most likely effective treatment regimen for the individual patient. In patients undergoing neoadjuvant chemotherapy, molecular analyses will be performed on biopsy specimens in order to obtain data that will be correlated to the treatment response. Additionally, ctDNA will be evaluated at three and six months post-treatment to assess biological response and its correlation with clinical and oncological outcomes. The collected data, which will encompass anthropometric and clinical factors, will be utilized to develop an AI-driven predictive algorithm regarding the efficacy and feasibility of subsequent surgical resection. Following surgery, patient-derived organoids will be established to test potential therapies in case of relapse and test the treatment administered. For patients who underwent neoadjuvant therapy, treatment response data will be recorded, while relapse-free survival and overall survival will be tracked for the entire cohort. Finally, a comprehensive analysis of all intra-cohort data will be performed, stratified by the two cohorts (upfront resection and neoadjuvant therapy), in order to evaluate the ability of ctDNA, organoids, and AI algorithms to predict clinical outcomes and to identify the cases in which these data could have changed the clinical approach. In these specific cases, the potential outcomes that would have been achieved by following the treatment algorithm suggested by these new factors will also be evaluated using entropy balancing.

Expected Impact

The goal is to establish a standardized methodology that could potentially ensure a tailored therapeutic pathway for every patient with pancreatic adenocarcinoma, thereby significantly improving the overall survival of this population. By applying the most advanced methodologies currently available, we expect that this exploratory study will define the potential, limitations, and applicability of this personalized approach. By doing so, we aim to precisely map out a pathway to optimize oncological outcomes for patients with pancreatic adenocarcinoma and validate it in a prospective setting. This approach aims to surpass current benchmarks in the literature, which typically rely on randomized comparisons of predefined therapeutic strategies. Should this study yield the anticipated results by demonstrating a possible improvement in the personalized treatment group, these findings will be validated in a prospective randomized trial comparing them against the current standard of care in order to challenge the current treatment algorithms and clinical guidelines. Furthermore, if prospectively validated, such evidence could support their inclusion in the standard Levels of Care recognized by the Italian National Health Service for pancreatic adenocarcinoma.



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The routine implementation of a tailored clinical approach holds the potential to improve outcomes not only from a clinical perspective but also from a socio-economic standpoint. By minimizing suboptimal therapeutic pathways, this strategy could also reduce the time-to-treatment, limit exposure to avoidable complications and adverse reactions, and ultimately decrease the overall economic burden on the healthcare system.

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