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EDITORIAL AND COMMENTARY

REDISCOVER the change in surgical management of pancreatic cancer from anatomy to biology

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The new REDISCOVER guidelines addressing borderline-resectable (BR-PDAC) and locally advanced pancreatic ductal adenocarcinoma (LA-PDAC) help to outline and summarize the challenges brought about by the treatment paradigm shifts that have occurred throughout the last decade [1, 2]. The advent of improved systemic therapy, optimization of surgical techniques, and the global shift from anatomical constraints to a more sophisticated classification based on tumor biology have brought up more questions than answers. The 34 recommendations from the REDISCOVER guidelines can be grouped into 8 pivotal areas which were constructed by 136 experts from 18 countries based on the existing literature. Despite the extraordinary expertise involved in the creation of the guidelines, the low level of evidence supporting the majority of recommendations highlights the urgent need for clinical trials and rigorous fundamental research in this patient population.

There is worldwide consensus that neoadjuvant therapy is optimal in the setting of borderline-resectable and locally advanced PDAC and that multiagent chemotherapy is superior to single-agent chemotherapy. Inadequate data are currently available to determine the optimal neoadjuvant therapy regimen. Whether neoadjuvant FOLFIRINOX or gemcitabine/nab-paclitaxel is superior has not been evaluated in a Phase III clinical trial. Phase II trials have demonstrated no significant increase in operative morbidity or mortality for 8 cycles of neoadjuvant FOLFIRINOX and chemoradiation therapy for patients with borderline-resectable and locally advanced PDAC [3]. Multiagent chemotherapy is preferred due to its improved efficacy; however, the increased morbidity and potential mortality cannot be dismissed. Therefore, the focus on number of cycles may not be the appropriate measure, but rather a cumulative dose of neoadjuvant chemotherapy which is able to consider not only the number of cycles but also the dose reductions which may occur due to toxicity. The inability to tolerate multiagent chemotherapy should not be underestimated and leads some patients to receive single-agent gemcitabine or 5-FU, despite decreased efficacy. In addition to systemic therapy, chemoradiation continues to be debated with significant practice differences throughout the world. The Alliance 021501 phase II randomized trial employed 8 cycles of mFOLFIRINOX as a neoadjuvant chemotherapy regimen for BR-PDAC and found that this regimen was superior to 7 cycles of mFOLFIRINOX followed by stereotactic body radiotherapy or hypofractionated image-guided radiotherapy [4]. This is the most recent trial to put radiation therapy into question for the treatment of PDAC. Currently, there are no evidence-based recommendations regarding the optimal regimen, cumulative chemotherapy dose received, or the timing of resection after neoadjuvant therapy due to the inability to consistently measure the biological response.

Previously imaging had provided a surrogate for biological response, but after neoadjuvant therapy, imaging is no longer reliable at predicting tumor response and resectability [5]. CA19-9 provides a helpful surrogate marker for the 90% of patients who produce the Sialyl Lewis A antigen (also known as CA19-9). In addition, CA125 provides prognostic information, especially in CA19-9 non-secretors [6]. While normalization of the marker portends a strong response to neoadjuvant therapy and hopefully an improved overall survival, the optimal decrease is unknown. A $\geq$ 50–85% reduction or a value $<$ 100 have been determined to be prognostically important in

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single-center studies, but many other studies have developed other unique prognostic algorithms. As the pancreatic cancer care community struggles to understand the biology of this aggressive disease, molecular testing is recommended by the NCCN guidelines. While the cost of testing to identify an actionable mutation is prohibitive for some health systems, the increasing body of knowledge gained through molecular testing will allow us a better understanding of patient subpopulations and their responses to therapy and should continue to be performed [7]. With the uncertainty of being able to measure the true biological response of PDAC to neoadjuvant therapy, the aggressiveness of the surgical approach remains to be studied.

The worldwide experts who participated in developing the REDISCOVER guidelines recommended that technically demanding operations involving divestment or resection and reconstruction of critical vessels should be performed in high-volume centers due to the high risk of morbidity and mortality [1]. The consensus recommended that these resections should be conducted at specialized centers named as 'centers of excellence'. It was noted that volume alone (i.e., the traditional concept of high-volume) might be inadequate for managing cancer growth around vessels. Preliminary evidence suggests that arterial resection and/or divestment may improve survival in selected patients, although the evidence remains limited and long-term survival outcomes cannot be reliably predicted for individual patients [8]. Technical questions regarding vascular conduits and anticoagulation also need further investigation. Yet, beyond the technical and logistical questions to optimize the surgical outcomes, we need a better understanding of which patients will actually benefit from aggressive local approaches. An aggressive local approach can only be justified in the setting of systemic disease control. An understanding and control of tumor biology is of utmost importance as approximately 80% of patients after pancreatic resection, with or without neoadjuvant therapy, recur distantly as their first site of recurrence [9]. For approximately 20% of the patients who have a more locally aggressive disease, an aggressive surgical approach may be justified including resection and reconstruction of essential visceral vessels after neoadjuvant therapy. For patients with a strong propensity for distant metastasis, an overly aggressive local approach may not be justifiable. Understanding genomic signals and molecular determinants of locoregional and distant disease progression will support informed decisions for appropriately aggressive surgical approaches.

The worldwide experts have provided a consensus document highlighting the challenges being faced in the care of patients with borderline-resectable and locally advanced pancreatic cancer. The 8 pivotal areas and 34 recommendations provide a summary of the many unanswered questions that remain in our treatment paradigms. The REDISCOVER guidelines motivate us to develop well thought out clinical trials and translational research to better understand the biology of pancreatic adenocarcinoma.

The pancreatic cancer care community should consider participating in the REDISCOVER registry (https://rediscover.unipi.it/) which facilitates comprehensive data collection on an "intention-to-treat" basis.

Data availability Not applicable.

Declarations

Ethical Standards, Research involving human participants and/or animals, and Informed consent Not applicable.

Conflict of interest None.

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