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EDITORIAL AND COMMENTARY

Pancreatic ductal adenocarcinoma: time for a neoadjuvant revolution?

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In his landmark publication "The structure of scientific revolutions" Harvard Philosopher Thomas Kuhn challenged the traditional view of science as the progressive accumulation of knowledge, and affirmed the concept of "progress through revolutions". In this framework, the reiteration of anomalies within a given conceptual network triggers a crisis whereby the underlying assumptions of the field are reexamined and a new paradigm is established. Maybe for the first time in the management of pancreatic ductal adenocarcinoma (PDAC), we are standing on the edge of such revolutionary shift.

The traditional paradigm of PDAC treatment is condensed in the well-known adage: "Surgery represents the only chance of cure for PDAC", which marks the introduction of most surgical research papers of the last decades. Given an aggressive malignancy diagnosed at an early stage so that surgery is feasible, would it not sound somewhat foolish not to resect it as soon as possible? Yet, this surgery-first approach recently began to falter. A deeper understanding of the biological nature of PDAC led to envision systemic spreading as an inherent feature of the tumor very early in its natural history. This is in line with the clinical observation that around 20% of the patients experience recurrence within six months, 40% within the first year after surgery, even in the case of a margin-free resection [1]. In this light surgery, albeit extensive, has no means to ensure a proper tumor clearance, advocating for a multimodal treatment approach. However, an increasing body of pragmatic evidence demonstrated that postoperative morbidity, performance status deterioration, and immediate recurrence might impair access to adjuvant therapy in up to one third of resected patients, hindering the delivery of this—yet crucial—multimodality [2].

Newly introduced chemotherapy regimens, such as FOLFIRINOX and Gemcitabine plus Nab–paclitaxel recently exhibited favorable results in advanced settings [3, 4], granting a proportion of locally advanced (LA) and even metastatic patients with surgical opportunity, with resection rates ranging between 0–40% for LA [4] and 4–9% for initially metastatic PDAC [5]. This fostered interest in their possible implementation within a neoadjuvant treatment (NAT) framework. According to the National Cancer Institute Dictionary, NAT is "a treatment given as a first step to shrink a tumor before the main treatment, which is usually surgery, is given" so that this term should be rightfully referred only to resectable (R) or borderline resectable (BR) patients. The putative advantages of NAT are multifold. Its primary aim is to downstage and/or downsize the tumor, increasing the likelihood of a margin-free resection. Moreover, NAT could be theoretically offered to a greater number of patients relative to adjuvant therapy because of its early administration in subjects with a better performance status than those who have received resection. Another possible benefit of NAT is the timely treatment of radiologically occult micrometastases. Its administration is also thought to exert a selection effect by enucleating patients with either aggressive tumor biology or low physiologic resilience, and spare them the risks of a highly morbid operation.

Level I evidence comparing the outcomes of NAT with upfront surgery for R and BR patients is limited, with only three fully published manuscripts available [6–8]. Nonetheless, results appear encouraging, with slightly lower resection rates but longer survival after NAT (Table 1). While the full results of ongoing trials [9] are eagerly awaited, the steady uptake of NAT is already shifting the paradigm of PDAC management. At our Institution, the proportion of patients receiving chemotherapy ± radiation prior to pancreatectomy has risen from < 15% before 2013 to > 50% in 2019. Notably, more than one third of these have a radiologically resectable disease at diagnosis.

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Table 1 Currently available phase II/III randomized controlled trials comparing upfront surgery versus neoadjuvant therapy in the treatment of borderline resectable and resectable pancreatic cancer

Author	Trial acronym	Publication	Type of RCT	Country of origin	Patient cohort	Treatment algorithm		Outcomes	
						Neoadjuvant treatment	Upfront surgery	Neoadjuvant treatment	Upfront surgery
Reni et al.	PACT-15	Lancet Gastroenterology and Hepatology 2018	Phase II, Multicentric	Italy	R	PEXG 3 cycles + surgery + PEXG 3 cycles $n=30$	Surgery + PEXG 6 cycles $n=30$[a]	Resection rate 84% 1-year EFS 66% Median OS 38.2 months	Resection rate 90% 1-year EFS 50% Median OS 26.4 months
Jang et al.	–	Annals of Surgery 2018	Phase II, Multicentric	Korea	BR	Gemcitabine-based chemoradiation (6 weeks) + surgery + mantainance gemcitabine (4 cycles) $n=30$	Surgery + gemcitabine-based chemoradiation (6 weeks) + mantainance gemcitabine (4 cycles) $n=28$	Resection rate 80% 2-year OS 41% Median OS 21 months	Resection rate 82% 2-year OS 26% Median OS 12 months
Versteijne et al.	PREOPANC-1	Journal of clinical oncology	Phase III, Multicentric	The Netherlands	R/BR	Gemcitabine-based chemoradiation (10 weeks) + surgery + gemcitabine (4 cycles) $n=119$	Surgery + gemcitabine (4 cycles) $n=127$	Resection rate 61% Median OS 16 months (per protocol 35 months)	Resection rate 72% Median OS 14 months (per protocol 20 months)
Sohal et al.	PREP-02/JSAC-05	ASCO 2019 (abstract)	Phase III, Multicentric	Japan	R	Gemcitabine + S-1 (2 cycles) + surgery + S-1 (6 cycles) $n=180$	Surgery + S-1 (6 cycles) $n=182$	Resection rate comparable (NR) Median OS 36.7 months	Resection rate comparable (NR) Median OS 26.6 months

EFS event free survival, *OS* overall survival, *R* resectable, *BR* borderline resectable, *NR* not reported

[a]Results regarding the third study arm (upfront surgery + adjuvant Gemcitabine are not displayed)

That considered, should a neoadjuvant-always approach become the new standard of care for PDAC? Indeed, evidence is not mature yet to answer this question, and the assumptions regarding the possible advantages of NAT remain largely speculative. Most of our knowledge is derived from surgical series, where the denominator is represented by the bulk of surgically explored patients and not by the total number of PDAC diagnoses. Consequently, there is little information on patients who were recommended NAT with intent for later resection but did not ultimately receive surgery (e.g., due to disease progression or decline in performance status during treatment). In a recent observational analysis of 614 LA and BR patients who were recommended primary chemotherapy at our Institution between 2013–2015, only 93% actually received and 72% completed the treatment. In this real-life snapshot, the resection rate was 15% in the overall cohort, rising up to 53% in the subgroup of younger patients with anatomically BR disease who completed FOLFIRINOX [10]. Whether this should be looked at as a positive selection effect—as patients who progressed or declined during NAT would have experienced early recurrence or impaired access to adjuvant therapy after upfront surgery—is impossible to ascertain. Moreover, complications associated with cyto-histological confirmation and/or biliary decompression before or during NAT might significantly hinder surgical eligibility. Other controversial issues regard the preferable treatment regimens and the role of complementary radiation therapy. Also the optimal duration and the selection criteria for surgery after NAT remain undisclosed, with significant variability between institutions. Notably, these controversies can hardly be solved only relying on randomized evidence. In real-world conditions, a sizable amount of patients are elderly or present with certain conditions (e.g., jaundice, comorbidities, deteriorated performance status) that may preclude treatment eligibility and enrollment in research protocols. This is testified by the extremely low enrollment rate of current trials of NAT [7, 8], suggesting strict patients selection and questioning the degree to which their results can be translated to the everyday practice. Well-designed observational studies appear of great importance to acquire pragmatic information on the effects of NAT at the population level.

In the end, although at the Verona Pancreas Institute we do embrace the current neoadjuvant revolution, this is not with blind enthusiasm. While the majority of patients harbor a systemic disease already at the time of diagnosis and would benefit from receiving systemic treatment first-line, there likely are a number of subjects who might have a different disease biology and would gain more advantage from an upfront resection. How to segregate the two scenarios remains however undisclosed. As per international guidelines [11], we currently recommend NAT to all BR PDAC and also to R patients exhibiting risk features such as high Ca19.9 serum levels, tumor contact with major vessels, suspect of metastases or distant lymph node involvement, and/or poor performance status. Yet, we must acknowledge that from a biological standpoint the value of classifications based on the degree of vascular involvement is almost nil. This is even truer considering that vascular resections—at least involving major veins—can now be performed with acceptable morbidity. In this setting, adopting different treatment modalities for R and BR is at best unwarranted.

If treatment allocation is currently mainly based on clinical, biochemical, and radiologic features, looking forward the nearest challenge appears to be the identification of new tools to better predict tumor response and develop personalized patient management pathways. Novel biomarkers such as circulating tumor cells, DNA and exosomes are currently scrutinized and their clinical implementation is forthcoming. PDAC management is moving from a radiology-driven to a biology-driven decision-making, whereby the treatment strategy and the degree of surgical aggressiveness will not anymore be based on anatomical classification but tailored to each tumor's specific genetic and molecular characteristics. Paradoxically, in the current era of extreme surgical proficiency, whereby technically almost anything is possible, our goal as pancreatic surgeons appears not to resect the largest number of patients, but to improve the identification of those who will truly benefit from our intervention. In this selected group, we should have the courage to push our resection beyond the borders of our best surgical technique. In these times of revolutions, let us envision two new surgical hashtags: #SelectBetter, #BeBraveAfterChemotherapy.

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