Visceral Medicine

Review Article

Visc Med 2022;38:37–41
DOI: 10.1159/000519755

Received: June 3, 2021
Accepted: September 17, 2021
Published online: October 26, 2021

# Molecular Profiling in Pancreatic Cancer: Current Role and Its Impact on Primary Surgery

Carmen Mota Reyes[a, b, c] Alper Doğruöz[a, d] Rouzanna Istvanffy[a, b, c]
Helmut Friess[a, b, c] Güralp O. Ceyhan[d] Ihsan Ekin Demir[a, b, c, d, e]

[a]Department of Surgery, Klinikum Rechts der Isar, Technical University of Munich, School of Medicine, Munich, Germany; [b]German Cancer Consortium (DKTK), Partner Site, Munich, Germany; [c]CRC 1321 Modelling and Targeting Pancreatic Cancer, Munich, Germany; [d]Department of General Surgery, HPB-Unit, School of Medicine, Acibadem Mehmet Ali Aydinlar University, Istanbul, Turkey; [e]Else Kröner Clinician Scientist Professor for Translational Pancreatic Surgery, Munich, Germany

**Keywords**
Molecular subtype · Pancreatic cancer · Primary · Neoadjuvant surgery

**Abstract**
***Background:*** The advent of next-generation sequencing technologies has enabled the identification of molecular subtypes of pancreatic ductal adenocarcinoma (PDAC) with different biological traits and clinically targetable features. ***Summary:*** Although current chemotherapy trials are currently exploiting this knowledge, these molecular subtypes have not yet sufficiently caught the attention of surgeons. In fact, integration of these molecular subtypes into the timing of surgery can in theory improve patient outcome. Here, we present the molecular subtypes of PDAC from the surgeon's perspective and a clinically applicable algorithm that integrates the molecular subtyping of PDAC preoperatively into the decision of primary surgery versus neoadjuvant therapy. Furthermore, we point out the potential of "tailored" (in addition to conventional) neoadjuvant treatment for exploiting the molecular subtypes of PDAC. ***Key Messages:*** We believe that for surgeons, the preoperative knowledge on the subtype of PDAC can properly guide in deciding between upfront surgery versus neoadjuvant treatment for improving patient outcome.


## Introduction

Outcomes for patients with pancreatic ductal adenocarcinoma (PDAC), even after margin-free resection, remain poor [1]. Accumulating data of the molecular pathophysiology of PDAC and advances in next-generation sequencing (NGS) have led to the discovery of actionable targets and to the definition of prognostic molecular-based subtypes with distinct biology and therapeutic susceptibility [2]. Such a classification has the potential to guide preclinical drug development, optimize risk assessment, and ultimately define individual treatment planning in patients with PDAC [2]. Single-gene mutations have already influenced surgical decision-making on a variety of solid tumors such as breast, lung, or colon cancer; in pancreatic cancer, however, the impact of molecular profiling on surgical care is yet to be established [3].

Multi-omics platforms have revealed a large portion of targetable molecular alterations that go beyond the well-known frequently mutated genes (*KRAS, TP53*, *CDKN2A*, and *SMAD4*) found in most pancreatic cancers [2]. Commonly altered pathways include DNA damage repair (15%), cell cycle (11%), and AKT/mTOR (19%) [4] (Fig. 1). Molecular-driven therapies have demonstrated already prognostic relevance since significant

karger@karger.com
www.karger.com/vis

Correspondence to:
Ihsan Ekin Demir, ekin.demir@tum.de

Karger

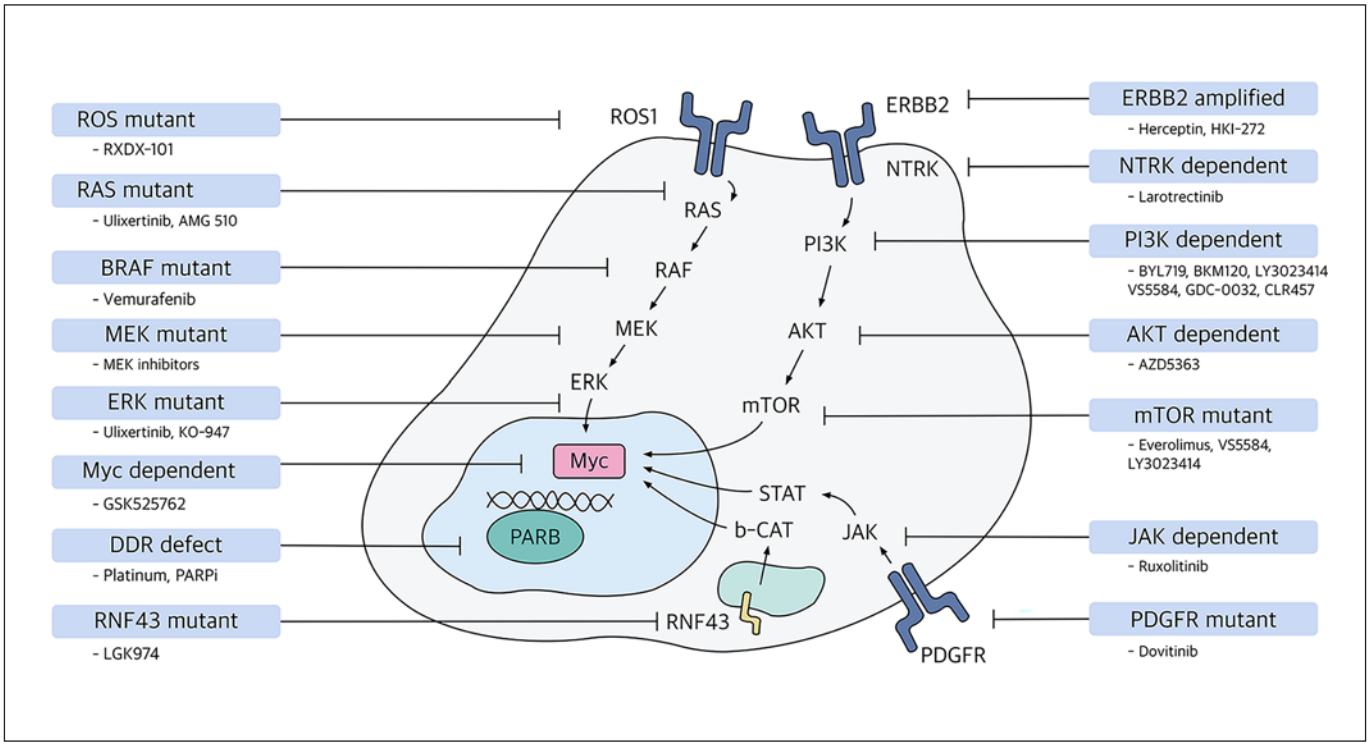


**Fig. 1.** Molecularly driven actionable strategies in pancreatic cancer. DDR, DNA damage response; EGFR, epidermal growth factor; mTOR, mechanistic target of rapamycin; NTRK, neurotrophic receptor tyrosine kinase; PARPi, PARP inhibitor, PI3K, phosphoinositide 3-kinase; PDGFR, platelet-derived growth factor receptor.

survival benefit has been recorded with immune checkpoint inhibitors for mismatch repair-deficient tumors and TRK inhibitors for tumors harboring *ROS1, NTRK1, NTRK2*, and *NTRK3* gene fusions [5]. In addition, pancreatic tumors driven by $BRAF^{V600E}$ mutation might benefit from treatment with RAF-MEK-targeted therapy [5]. Finally, germline and somatic mutations in DNA damage repair genes such as *BRCA1* and *BRCA2* have notably responded to platinum-based chemotherapy and single-agent poly-(ADP-ribose) polymerase inhibition [5–7]. The Know Your Tumor (KYT) program enabled pancreatic cancer patients to undergo multi-omics profiling and provided recommendations for molecularly rationalized clinical trials and personalized off-label therapy [4, 5]. The results of this trial demonstrated that patients with actionable genomic alterations can considerably profit from receiving a matched therapy, with over 1-year survival benefit compared to patients with targetable mutations that received unmatched therapies [5]. However, single actionable somatic mutations are unlikely to suffice at providing survival advantages or clinical predictive value, as already shown by exome sequencing of long-term PDAC survivors [8], though patterns of mutations in multiple genes may stratify PDAC prognostically and guide combinational treatment management [9].

## Molecular Tumor Taxonomy in PDAC

Molecular tumor taxonomy is an emerging research area, and over the past years, a plethora of subtyping schemes for primary resected pancreatic cancer have been proposed [10]. Collison et al. [11] were the first to describe 3 transcriptional subtypes with prognostic and biological relevance including quasi-mesenchymal, classical, and exocrine-like [10, 11]. In 2015, Moffitt et al. [12] defined 2 tumor subtypes, which they termed basal-like and classical, and in a subsequent study, Bailey et al. [13] described 4 gene expression subtypes of pancreatic cancer: squamous, pancreatic progenitor, immunogenic, and aberrantly differentiated endocrine exocrine (ADEX) [10, 12, 13]. The basal-like, squamous, and quasi-mesenchymal PDA subtypes overlap directly across all 3 classification systems and are associated with a poor prognosis and with mutations in genes involved in DNA methylation [2]. The Bailey et al. [13] pancreatic progenitor subtype and Collisson et al. [11] classical group largely overlapped with the classical samples defined by Moffit et al. [12] and in contrast to the squamous subtype, these are primarily defined by pathways and networks involved in pancreatic endodermal differentiation and are associated with better survival [6]. In the COMPASS trial, basal-like tumors showed a lower radiographical response to first-line chemotherapy, supporting a potential predictive role

of transcriptional-based subtypes, particularly for therapy-resistant borderline resectable patients that may benefit from primary resection rather than neoadjuvantly intended approaches [1]. Importantly, basal-like tumors showed resistance to FOLFIRINOX, paclitaxel, and tyrosine kinase inhibitors, and the classical transcriptional subtype, on the contrary, showed increased susceptibility for EGFR inhibition by erlotinib [1, 10]. These findings strongly support the need to incorporate molecular subtyping in therapy decision-making in patients with PDAC [1, 10].

Transcriptomic data are well suited for subtype classification of pancreatic cancer, compared with genomic and methylome data, which are currently scarce and difficult to interpret [2]. Transcriptional profiling based on the expression of coding genes is, however, only one of many ways of subtyping [2]. The Cancer Genome Atlas (TCGA) pursues an integrative multiplatform molecular analysis that merges different layers of omics data and the use of other factors impacting gene expression, such as noncoding RNA expression, DNA methylation, or proteomics [2, 6]. As a result, they found that high-purity tumors cluster into a basal-like/squamous group and a classical/progenitor group and attributed the immunogenic and ADEX or exocrine-like subclasses found by Bailey et al. [13] and Collison et al. [11] to confounding transcripts from nonneoplastic cells [6]. A more global approach combining proteomic analysis with RNA classification and integrating this with the immunological signatures and stroma is also surely relevant at defining clinically relevant pancreatic cancer subtypes [2].

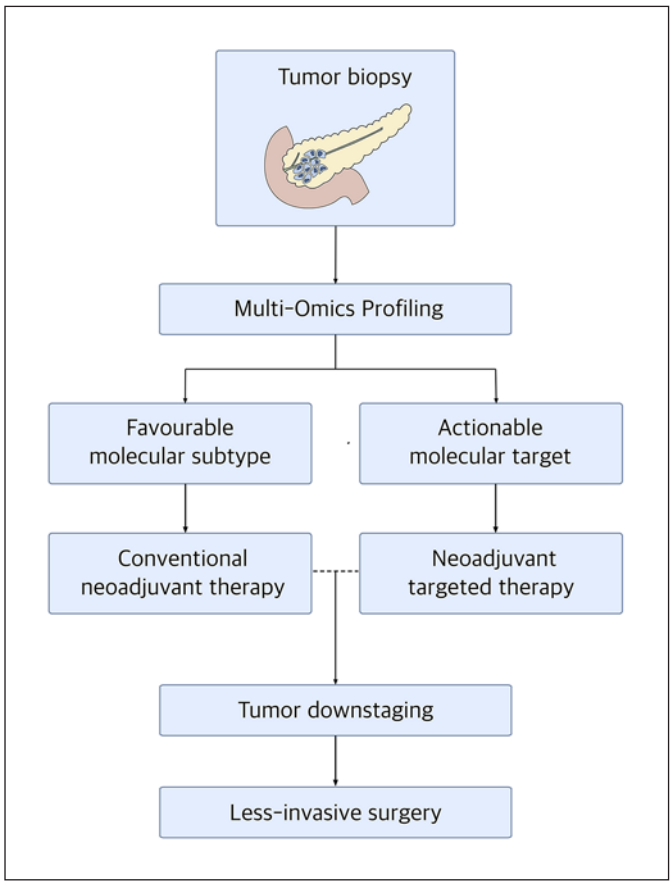


**Fig. 2.** Impact of molecular profiling on primary surgery in PDAC. Here, we propose a novel algorithm for upcoming multidisciplinary trials that can integrate the knowledge on the molecular subtypes of PDAC into the treatment of patients with resectable and/or borderline resectable PDAC. PDAC, pancreatic ductal adenocarcinoma.

## Challenges in Front of Translating Molecular Subtypes of PDAC into the Clinical Practice

The translation of these molecular PDAC subclasses into the routine clinical practice is still in its infancy, and although over 25% of pancreatic tumors harbor actionable mutations that could potentially confer eligibility for clinically available targeted therapies, <5% of patients were able to receive targeted therapies on the KYT program [5]. The implementation of precision oncology in pancreatic cancer is challenging due, among other reasons, to the aggressiveness of the disease and the need of early induction of systemic therapy [5]. This might hamper first-line molecular-driven treatments that currently need a timeframe between 2 and 8 weeks from sample acquisition to clinical reporting and therapy start [1, 14]. Further obstacles to the widespread adoption of clinical NGS include the high economic costs of molecular profiling and the difficulties on the acquisition of sufficient amounts of cancer tissue for sequencing procedures [1]. The latter has been overcome by the development of single-sample classifiers able to reliably identify the 2 intrinsic pancreatic tumor subtypes even from small sample biopsies obtained by fine-needle aspiration [10]. Targeted neoadjuvant treatment, based on biopsy multi-omic profiling, might further downsize the tumor compared to conventional neoadjuvant approaches with consequently higher rate of R0 resection, diminished need for vascular resection, and potentially decreased rates of local recurrence [3]. Current evidence from the PREOPANC trial supports the administration of neoadjuvant therapy to patients with borderline resectable pancreatic cancer due to improved R0 resection rate, with, however, potentially more toxicity when compared to primary surgery [15]. Last, the intratumoral heterogeneity of PDAC might contribute to a misleading tumor subtype and unreliable clinical prognostication [3]. A potential solution is an increased sampling from several locations throughout the tumor which, due to the technical difficulty of pancreatic biopsies' acquisition and a higher risk of tumor seeding, will need further optimization.

## Improving the Outcome of Resectable PDAC through Molecular Subtyping

Clinical translation of NGS and molecular subtyping of PDAC may ameliorate disease outcomes enabling precision oncology therapy in selected patients and tailoring treatment strategies for the different subgroups. With decreasing costs, a more accessible technology, and the possibility of NGS of nonsurgical tumor biopsies, the idea of clinical genomic sequencing will be undoubtedly no longer restrained to investigational settings in the near future. Resectable and borderline resectable pancreatic tumors might particularly benefit from molecular-driven approaches owing to a lower tumor load in the neoadjuvant setting and after surgical resection due to preclinical target discovery and a molecularly guided adjuvant therapy [14, 16] (Fig. 2). Unfavorable transcriptional tumor subtypes and the lack of actionable somatic mutations may tip the balance for primary resection, avoiding the morbidity of systemic therapy and surgery delay in selected primary resectable patients with PDAC.

In current clinical practice, surgery is still the most important cornerstone of pancreatic cancer treatment [3]. Although conventional neoadjuvant therapy has been able to downstage tumors in locally advanced and borderline resectable tumors, multi-omics tumor profiling of tumor biopsies before targeted neoadjuvant treatment has shown great promise and may result in optimal patient selection for systemic therapies, less-extensive surgical procedures due to maximized tumor shrinkage, or even lead, in the long term, to a wait-and-see approach in patients with PDAC with complete response to molecular-driven therapies [3]. We have recently reviewed and summarized the currently ongoing trials employing neoadjuvant therapy in human PDAC [17].

## Conclusion

From the surgeon's perspective, the molecular subtypes of PDAC currently have no routine clinical utility. However, we believe that this is subject to change, as determining the molecular subtypes of PDAC through extensive pre- or intraoperative biopsy sampling can help in optimal patient selection for neoadjuvant therapy and thereby avoid extensive resection and improve patient outcome. Patients with no molecularly actionable subtypes may be more liberally considered for primary resection. Moreover, the implications of molecular subtypes of PDAC await testing for the adjuvant setting after primary resection, as certain subtypes may in theory better respond to postoperative treatment. Therefore, we plea for integrating the molecular subtypes of PDAC into upcoming multidisciplinary trials that will recruit resectable and/or borderline resectable PDAC.

## Conflict of Interest Statement

The authors have no conflicts of interest to declare.


## Funding Sources

I.E.D. was funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) – Project-ID 329628492 – SFB 1321.


## Author Contributions

I.E.D., H.F., and C.M.R. designed the content. C.M.R., A.D., and I.E.D. generated the first draft. R.I., G.O.C., and H.F. critically read and revised the manuscript. All authors have agreed on the final version of the manuscript.

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