Discussion: Current Multimodality Treatment Options in Pancreatic Cancer in Clinical Practice – What Is the Future Impact of Molecular Biological Profiling?

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Kleger and Kornmann: Do You Have Criteria Not to Resect the Tumor of a Patient Even If It Is Technically Resectable? Please Describe Them

Ellenrieder

Upfront surgery is the treatment of choice in clearly resectable PDAC. However, in borderline resectable PDAC, we would suggest a neoadjuvant treatment of 3 months. Neoadjuvant therapy in resectable PDAC is still being investigated in clinical trials. If a patient does not wish a resection to be performed or the patient's fitness is not suitable for surgery, PDAC will not be subject of a surgical approach.

Friess

Next to technical resectability, we consider the biological resectability. That is, if a patient has severe/advanced cardiac or pulmonary or other comorbidities, we do sometimes prefer not to resect the tumor, although it would be resectable. However, these cases are rare.

Kornmann

The sole criterion not to resect in this case would be excessive comorbidity and ECOG performance. Patients with high CA19-9 levels (>500 U/mL) are also recommended to undergo a form of “neoadjuvant” chemotherapy before reevaluation and possible resection.

Michl

Contraindications for surgery in resectable tumors include advanced (biological) age, poor general condition (ECOG >2), limiting comorbidities, especially when associated with excess CA19-9.

Schneider

In terms of disease-specific survival, pancreatic cancer patients generally benefit from surgical resection when complete resection can be achieved. We therefore generally recommend surgical exploration whenever complete resection appears to be technically feasible. We do however not resect patients with locally resectable tumors in presence of metastatic disease. An exemption are selected patients with oligometastatic disease and putatively favorable tumor biology, if metastatic lesions can be entirely resected.

Yang

(1) Radical resection cannot be performed in cases with distant metastasis, such as liver metastasis, lung metastasis, intraperitoneal implantation metastasis, etc. (2) The overall assessment of the patient, the ability to tolerate surgery, such as old age, weakness, and many severe diseases, can also be considered for nonoperative treatment. (3) The tumor invades the superior mesenteric artery more than 180°.

Kleger and Kornmann: In What Situations Do You Recommend to Perform Neoadjuvant Treatment?

Ellenrieder

We would recommend neoadjuvant treatment in borderline and nonresectable locally advanced PDAC. The role of surgery following neoadjuvant treatment for patients with oligometastatic disease is subject of investigation in ongoing clinical trials.

Friess

For sure in patients with locally advanced primarily nonresectable cases and in the majority of patients with borderline resectable cases.

Kornmann

We would strictly follow the recently updated German S3 guidelines, which recommend neoadjuvant treatment in case of a borderline resectable or locally advanced pancreatic cancer. Here, the group of borderline resectable cases is subdivided according to anatomical and biological criteria, the latter comprising resectable cases with CA19-9 values at primary diagnosis above 500 U/mL.

Michl

Arterial involvement (LAPC) is a clear indication for neoadjuvant treatment. In patients with borderline resectable tumors with venous involvement, we increasingly offer neoadjuvant therapy, preferentially with mFOL-FIRINOX.

Schneider

We generally aim for upfront resection in patients with resectable or borderline resectable pancreatic adenocarcinoma. We recommend neoadjuvant treatment in locally advanced pancreatic cancer that is not initially resectable due to broad involvement of the superior mesenteric artery or coeliac axis. In these patients, we aim for secondary resection, which may be facilitated by advanced surgical techniques such as arterial divestment or arterial resection and reconstruction as applicable (i.e., in selected patients with otherwise favorable general health status).

Yang

Borderline resectable pancreatic cancer. Resectable pancreatic cancer with regional lymph node metastasis or larger tumor size. For resectable pancreatic cancer, when CA19-9 is at a high level, such as more than 1,000 U/mL, we consider giving priority to neoadjuvant chemotherapy. For stage T4 pancreatic cancer, technically, we can reconstruct the arteries or veins to ensure a negative margin, but we usually choose neoadjuvant chemotherapy.

Kleger and Kornmann: Which Patients Do You Send to Exploration after Neoadjuvant Treatment and Which Patients Should Not Undergo Exploration?

Ellenrieder

If neoadjuvant therapy results in tumor response and there are no evident metastases, exploration will be suggested. In the case of local progression after therapy or in case of metastasis, patients should not undergo exploration.

Friess

Patients with locally advanced or borderline PDAC, whose tumor has not grown during neoadjuvant treatment, are sent for exploration. We refrain from exploring if (1) the tumor has grown further, (2) the patient exhibits metastasis after the neoadjuvant treatment, and/or (3) the serum CA19-9 value has substantially increased during therapy.

Kornmann

Every patient without signs disease progression should undergo exploration. CT-based judgment of resectability after neoadjuvant treatment frequently underestimates tumor response upon chemotherapy albeit proper resection would be technically possible.

Michl

We recommend surgical exploration to all patients which respond biochemically and by imaging. Also, patients which respond to neoadjuvant treatment clinically and biochemically but are stable by imaging will usually receive counseling for surgical exploration. Only patients with clear clinical deterioration, biochemical progress, and/or progression by imaging will continue to receive palliative chemotherapy.

Schneider

Since viable tumor residues cannot be reliably discerned from residual scar tissue based on radiologic characteristics, we generally favor surgical exploration with frozen sections from suspicious periarterial tissue in order to determine secondary resectability after (extended)

neoadjuvant treatment. We thus recommend exploration whenever neoadjuvant treatment results in tumor regression or at least stable disease and in the absence of distant metastases.

Yang

After neoadjuvant chemotherapy, if the tumor has no distant metastasis and the imaging evaluation of the tumor is PR or SD. We will carry out surgical exploration. For borderline resectable or locally advanced pancreatic cancer, CA19-9 decreased significantly after neoadjuvant chemotherapy, and surgical exploration can also be considered.

Kleger and Kornmann: When Do You Perform Surgery in Patients with Recurrence at Your Institution?

Ellenrieder

In local tumor recurrence, usually, chemotherapy or chemoradiation will be started. If there is a response to this therapy and tumor burden is low, patients can undergo secondary resection as an individual treatment concept.

Friess

We resect these tumors if the recurrence is locally resectable and has developed late after the primary resection. We normally do an induction chemotherapy and if the recurrence has responded or remained stable during “induction” chemo- or radiotherapy and if the patient has no further metastatic lesions, we go for an exploration.

Kornmann

Individual patients in good condition with localized recurrence or a solitary metastasis are candidates for such surgery with a potential benefit.

Michl

If recurrence occurs after a longer period of time (usually >1 year) indicating a moderate tumor biology, if recurrence occurs at a surgically resectable location (e.g., lymph node recurrence), and if patients are considered fit enough, surgery for recurrence is considered. This is usually done after several courses of induction chemotherapy to select for patients with a favorable tumor biology and to avoid surgery in patients with rapid tumor progression.

Schneider

In our experience, patients benefit from resection of isolated recurrence when tumor biology is favorable, as indicated by an extended time interval (>10–12 months)

from initial resection to detection of recurrence, or by tumor response to preoperative chemotherapy.

Yang

For patients with recurrence, we firstly carry out abdominal enhanced CT and systemic PET-CT to determine the tumor load. If it is local recurrence, chemotherapy or radiotherapy should be given first and then reexamined after two cycles of treatment to clarify the effect of chemotherapy or radiotherapy. If the tumor has no progress with the CA19-9 decreasing significantly, surgical treatment can be considered at this time when the patient can tolerate the operation. Otherwise, surgery is not considered.

Kleger and Kornmann: Do You Already Include Individual Tumor Profiling Results to Support Patient Treatment?

Ellenrieder

Yes, we do. If there is response to FOLFIRINOX, we test for BRCA mutation or BRCAness and would include PARP inhibitor therapy in the treatment concept in case of pathogenic mutations of these genes. Additionally, we start molecular profiling for individual treatment concepts as soon as the patient proceeds for a second-line treatment, and patient fitness qualifies for more treatment options.

Friess

In our institution, this information is currently used for second- or third-line (chemo-) therapy planning.

Kleger

Currently, individual tumor profiling in a first-line setting is restricted to individuals under suspicion of a hereditary cancer syndrome due to family history or atypical clinical presentation. Genetic testing for germline BRCA1/2 mutations should be tailored for all advanced PDAC patients fit to undergo any cancer-specific therapy. In addition, a more comprehensive gene panel-based screening of tumor tissue should be part of molecular tumor board guided decision-making in specialized centers.

Michl

We usually perform NGS panel sequencing in younger patients with progression after standard 1st- and 2nd-line chemotherapy who are fit enough to undergo further experimental treatment. MSI and NTRK analyses are separately performed upfront, BRCA1/2 analyses in patients responding to platinum treatment.

Schneider

We believe that a reliable estimate of underlying tumor biology is crucial for surgical decision-making in locally advanced or recurrent pancreatic adenocarcinoma. However, currently available data on molecular pancreatic cancer subtypes and their prognostic relevance do in our view not outperform clinical parameters in this regard.

Yang

At present, we routinely carry out the next-generation sequencing analysis of pancreatic cancer patients to identify the reason that may cause tumors in patients, in order to guide their immediate family members to pay attention to this kind of disease. We try our best to find possible therapeutic targets through the sequencing results in order to achieve individualized treatment.

Kleger and Kornmann: In Which Field Do You See Most Potential for Further Treatment Individualization of Pancreatic Ductal Adenocarcinoma Patients?

Ellenrieder

According to current data, we see a benefit for precision oncology in a palliative setting.

Friess

We see a major potential in ex vivo drug testing using organoids, including preoperative testing (for neoadjuvant therapy) and postoperative testing (for adjuvant therapy).

Kleger

Approximately 14% of pancreatic cancers harbor mutations in genes ensuring appropriate DNA repair after damage, like the *BRCA 1* and *2* genes. Recently, with olaparib, a first treatment option for *BRCA 1* and *2* mutated pancreatic cancer was approved. However, there is a relevant proportion of further genes involved in the DNA damage repair beyond *BRCA1* and *2* that might benefit from such tailored therapeutic interventions like olaparib. Unfortunately, due to the lack of specific data, no general recommendations are currently available (PMID: 34503069, 32855305). However, targeting the DDR holds great promise to improve patients' prognosis in a midterm perspective.

Michl

In both neoadjuvant and adjuvant situations, personalized treatment based on molecular profiling will guide the choice of chemotherapy regimens in the foreseeable future. In the palliative setting, conventional panel sequencing will probably guide personalized therapy for a

small subset of patients. Further multi-omics profiles including epigenetic, transcriptomic, and possibly microbiome profiles will hopefully open further avenues in personalized palliative therapies.

Schneider

Multi-omics approaches, once reliably interpretable in terms of clinical outcomes, will potentially provide novel options to discern oligometastatic disease from cases characterized by rapid systemic spread. Such information may greatly facilitate individualized treatment decisions concerning radical local resection versus systemic therapy.

Yang

Pancreatic cancer is a kind of cold tumor, and the internal immune function is suppressed. Reactivating the recognition and killing effect of immune cells to tumor cells might be a breakthrough for the treatment of pancreatic cancer in future.

Kleger and Kornmann: Do You Consider the Suspicion of a Genetic Syndrome, e.g., Germline BRCA1/2 Mutation into Your Surgical Decision-Making?

Ellenrieder

Not yet.

Friess

It does not directly influence our surgical decision-making but certainly affects genetic counseling and the planning of 2nd-line therapies or maintenance therapy.

Kleger

Extension of testing to all settings of PDAC, including patients with resectable or borderline resectable PDAC, might be feasible also in case of neoadjuvant treatment strategies as retrospective data suggest an increase in complete pathologic responses after neoadjuvant FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan, and oxaliplatin) for *BRCA*-mutated PDAC patients in such situation (PMID: 32314163, 34503069). Definitive indications for g*BRCA1/2* testing in PDAC includes (i) cases with a positive family history for PDAC, (ii) previous *BRCA*-associated tumors, (iii) young age at the initial diagnosis, and (iv) in patients with a good response to platinum therapy.

Michl

We consider suspicion of a genetic syndrome as indication for genetic testing and counseling as well as thorough preoperative staging, but this does not affect surgical decision-making in a resectable situation.

Schneider

In presence of genetic syndromes facilitating pancreatic cancer development, we are more inclined to recommend resection of radiologically suspicious (i.e., cystic) lesions, which would otherwise justify a watch-and-wait concept. In all such cases, we aim for a balanced interdisciplinary treatment decision.

Yang

As mentioned above, our current routine next-generation sequencing of pancreatic cancer can help us identify germline BRCA1/2 mutations for individualized treatment.

Kleger and Kornmann: Which Preclinical Tool Do You Expect to Enter Clinical Routine First?

Ellenrieder

Drug testing in patient-derived organoids might be a helpful tool after analysis of genetic alterations in a precision oncology approach.

Friess

Ex vivo drug testing using organoids.

Kleger

Patient-derived organoid (PDO) models have proven as powerful tools in basic and translational research. PDOs represent a suitable method for ex vivo pharmacotyping within a reasonable time frame (PMID: 32657929). PDO-derived gene signatures in PDAC were found to predict chemotherapy sensitivity (PMID: 29853643) and in vitro drug responses correlated with clinical response in various patient examples in gastrointestinal cancers (PMID: 31818951). Moreover, a recent prospective trial evaluated the feasibility of PDOs as a preclinical tool for drug response prediction in a clinical routine setting and correlated the in vitro prediction with the therapeutic response in a representative cohort of PDAC patients (PMID: 34064221). Despite their great promise, some hurdles need to be overcome: (i) their culture lacks a proper tumor microenvironment and (ii) leads to transcriptomic shifts (PMID: 34064221). In the future, the employment and customization of hPDOs by TME-based modeling efforts as well as optimizing the drug screening format could overcome these remaining limitations.

Michl

Ex vivo analysis organoid/spheroid testing to predict chemotherapy sensitivity will be probably most useful in clinical decision-making and enter routine first once standardization has been achieved. Liquid biopsies using circulating DNA have prognostic value but are currently

less likely predictive to guide specific therapies (as compared to other tumor entities).

Schneider

Immunotherapy may become a game changer in multidisciplinary management of PDAC and further enhance surgical options for locally advanced or oligometastatic disease. For the time being, it remains essential to base clinical decision-making on thorough and multidisciplinary clinical assessment.

Yang

Pancreatic cancer is a highly malignant digestive tumor. Because of unspecific symptoms in early stage of pancreatic cancer, the vast majority of patients lost the opportunity of operation in the initial diagnosis. Therefore, we particularly hope to design early diagnostic reagents for pancreatic cancer, so as to improve the resectable rate of pancreatic cancer and prolong the survival of patients.

Conflict of Interest Statement

All the authors have no conflicts of interest to declare.

Chair

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