A novel event-free survival endpoint in locally advanced pancreatic cancer

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Abstract: The treatment paradigm for locally advanced pancreatic cancer (LAPC) is evolving rapidly. The development of neoadjuvant therapies composed of combination therapies and the evaluation of their impact on conversion to borderline resectable (BR) status, resection, and ultimately overall survival (OS) are presently being pursued. These efforts justify revisiting study endpoints in order to better predict therapeutic effects on OS, by capturing not only the achievement of R0 resection at the end of induction therapy but also the long-term reductions in the rate of local and distal recurrence. The proposed herein event-free survival (EFS) endpoint, with its novel definition specific to LAPC, is formulated to achieve these objectives. It is an analog to disease-free survival (DFS) endpoint in the adjuvant setting applied to the neoadjuvant setting and may be a valuable surrogate endpoint for this patient population.

Keywords: clinical trial endpoint, event-free survival, locally advanced pancreatic cancer, overall survival, pancreatic cancer

Introduction

About 30–40% of patients with pancreatic ductal adenocarcinoma (PDAC) have a locally advanced pancreatic cancer (LAPC) which is non-metastatic and limited to the pancreatic region, but unresectable due to involvement of major blood vessels. The recommended management in eligible patients consists of chemotherapy with 5-fluorouracil, irinotecan and oxaliplatin (FOLFIRINOX) or gemcitabine/nab-paclitaxel (G/NP) combinations potentially followed by chemoradiation depending on standard of care in specific institutions. While LAPC has an unfavorable prognosis, there are significant opportunities for providing patients with more substantive benefits than in the setting of metastatic PDAC for the following reasons: (1) this is an earlier stage of the disease, where survival ranges from 9 to 32 months across various studies, compared with 10–12 months in metastatic PDAC; (2) available options for effective therapeutics could be either prevention of local progression (increase in tumor size, often accompanied by recurrence of pain and increase in CA 19.9 level) or prevention of development of metastatic disease; and (3) a limited group of patients may be candidates for surgery after neoadjuvant treatment with the goal of achieving R0 resection. A decision to perform surgery is made on case-by-case basis and is usually based on the performance status, tumor shrinkage on imaging, and decrease in CA 19.9 level. Changes in standardized uptake values (SUVs) of positron emission tomography with 18 fluorodeoxyglucose (PET-18FDG) after neoadjuvant treatment can also be evaluated and taken into consideration. In some cases, local tumor can be completely removed with good histological results (i.e. R0 and N0).

Several predictive factors are taken into consideration when deciding on whether or not surgery should be performed in a specific patient post neoadjuvant therapy. For example, in a retrospective study by Chatzizacharias et al., authors classified patients into two groups: (1) LAPC type A, where surgery may be considered after systemic therapy and chemoradiation and (2) LAPC type B, where it would be unlikely to consider surgery post neoadjuvant treatment with combination chemotherapy. In this report, 62%
of type A and 24% of type B underwent a curative-intent resection with an overall R0 resection rate of 80%. On average, about a 25% overall resection rate, with a 78% R0 resection rate, has been reported in a systematic review of mainly retrospective published studies. Successful surgery achieving R0 resection may increase overall survival (OS) in these patients, and non-surgical ablative therapies in LAPC also are presently under investigation. For future clinical trials in this patient population, it is important that endpoints be identified that capture the clinical effects of neoadjuvant therapies as well as the effects of surgical resection in this setting.

Formulating a novel event-free survival endpoint for LAPC

There are many definitions of event-free survival (EFS) endpoints in the clinical literature. For example, the American Society of Clinical Oncology has defined EFS to be the time until tumors return or existing tumors progress, while the National Cancer Institute has provided an alternative definition of EFS as the length of time that the patient remains free of certain complications or events that the treatment was intended to prevent or delay. A majority of randomized clinical trials in oncology use OS as the primary endpoint, followed by progression-free survival (PFS), time to progression (TTP), and disease-free survival (DFS) as secondary endpoints. As outcomes, EFS and OS were similarly distributed in the metastatic and adjuvant setting, but PFS and TTP were more widely used in metastatic settings.

The events historically used in EFS endpoint include progression or the onset of certain symptoms, such as bone pain from bone metastases. In this section, we will define and discuss a novel EFS endpoint which may be used in future LAPC studies as surrogate endpoint for OS.

An important goal in clinical research is to reliably evaluate the safety and efficacy of interventions. In settings such as LAPC where the tumor can be removed surgically with good histological results after induction treatment (i.e. R0 and N0), clinical endpoints are needed that, when compared with the standard OS endpoint, would have enhanced sensitivity to the therapeutic benefits applied in the setting of LAPC (e.g. chemotherapy and surgery). Ideally, key endpoints in clinical trials should be direct measures regarding how a patient ‘feels, functions or survives’, such as effects on symptoms measured by patient-reported outcomes or on activities of normal daily living measured by clinician-reported outcomes or observer-reported outcomes, or on OS. Biomarkers that are properly validated as surrogate endpoints also could be used as registrational endpoints and may provide a basis for accelerated approval.

LAPC and metastatic pancreatic cancers have been pooled in numerous studies but their management and prognosis are different depending on the sites: use of neoadjuvant treatment, preference or not to do surgery, and so on. While OS is generally used as the primary endpoint of studies in metastatic PDAC, there is an increasing interest in the LAPC setting to identify an endpoint that would incorporate the outcome of surgery, while providing enhanced sensitivity to the impact of therapeutic measures, such as neoadjuvant treatment, on how patients feel and function, while still being sensitive to effects on their survival.

A classic example of a properly validated surrogate endpoint for ‘feels, functions, survives’ effects would be ‘recurrence-free survival’ or ‘disease-free survival (DFS)’ in an adjuvant setting. This is the time to first detection of residual disease or death post-surgery. In the neoadjuvant setting, or for hematologic malignancies or other settings where interventions such as drugs, biologics, radiation therapy, or surgery would be used to render a patient free of detectable disease after a well-defined induction/neo-adjuvant period, a logical extension of the validated concept of DFS would be a time-to-event endpoint, with failure defined to be the earliest of the occurrence of: (a) failure to achieve disease-free status locally at the end of the induction and surgery period; (b) detection of recurrence of disease (either local post induction or distal) by CT; or (c) death. Figure 1 provides a graphical summary of this definition of EFS.

This composite endpoint, which is a novel formulation of DFS applied in the neoadjuvant setting, seems particularly well suited to be a key measure of efficacy for therapeutic strategies in settings such as LAPC that may involve neoadjuvant treatment followed by surgery, with the goal of rendering such patients disease-free (locally and systemically). Unlike the DFS term, EFS would broadly address the clinically important considerations in neoadjuvant settings.
Arguments to further support the EFS endpoint in the LAPC setting
There are several reasons to justify the expectation that EFS would have value as a surrogate endpoint for effects on both quality of life (QOL) and OS in a setting such as LAPC. First, it is sensitive to effects on remission, and in particular complete remission that likely would have substantial clinical value. Patients who are in remission have a better QOL mostly related to decreased pain and fatigue, reduced frequency of transfusions, less time spent in hospital for treatment of infections, and a more positive view of their future. For example, several studies in melanoma have demonstrated improved QOL in patients who were free of disease. The recent FDA approvals of new drugs for colorectal cancer and adjuvant treatment of melanoma, despite a failure to improve OS, might serve as precedents for a similar approach in LAPC. A similar situation was observed in acute myelogenous leukemia (AML) where several drugs, later approved by the FDA, including clofarabine and sorafenib, have prolonged EFS but not OS, and the use of EFS as a basis for a new drug approval in AML led to additional therapeutic options for patients with AML. In addition, EFS may have particular sensitivity to the effects of the primary treatment relative to the effects of subsequent treatments that are given when the study drug fails.14 It has

Figure 1. Definition of EFS in LAPC.
to be noted that, in oncology, different versions of the EFS endpoint are already being used in about 7% of all oncology clinical trials, in about 25% of all clinical trials on leukemia, and for clinical trials in neuroblastoma, breast cancer, and lung cancer.

In general, when defining any composite time-to-event endpoint, this should not be configured too broadly such that the overall clinical relevance of the endpoint, enhanced by the more clinically important components, could then be diluted by inclusion of other less important components. For example, in a composite endpoint with ‘progression of major symptoms’, and ‘death’, clinical relevance would be reduced by the additional of components, ‘discontinuation of treatment’ or ‘exposure to rescue treatment’. The novel formulation of EFS proposed in this article has the benefit that all three components of its definition, that is, failure to achieve local disease-free status following surgery, or disease recurrence, or death, are all of compelling clinical importance to the patient. It has a key strength of being reasonably likely to predict therapeutic effects on OS, but also, in conjunction to data on symptomatic adverse events, it provides enhanced sensitivity to therapeutic effects on QOL.

Table 1 summarizes main studies of hematological malignancies reporting EFS.

**Statistical justifications for the novel definition of EFS**

A clinically meaningful endpoint in the LAPC patient population, such as OS, would be influenced not only by local disease, including its future seeding of metastatic disease, but also by any undetected metastatic disease or micro metastases. A therapeutic strategy involves the addition of any drug that has the potential to favorably affect both local and metastatic diseases. While achieving R0 is relevant, focusing on this alone captures only the effect of the drug (and surgical skill, perhaps) on controlling local disease. It is therefore proposed that R0 resection rates be evaluated in the larger context of a DFS/EFS type of endpoint, which might be useful as a surrogate endpoint to support accelerated approval. A carefully defined DFS/EFS type of endpoint can capture not only the effects on achieving R0 resection but also effects on metastatic disease, making it more likely that effects on this endpoint would be reasonably likely to predict effects on QOL and OS.

In the novel formulation of EFS considered in this article, the validated concept of DFS from the adjuvant setting is logically extended to the neoadjuvant setting where initial neoadjuvant therapy, potentially including surgery in eligible patients, could render a patient to be free of disease. As indicated earlier, failure is defined to be the earliest of the occurrence of: (a) failure to achieve disease-free status locally at the end of the induction and surgery period; (b) detection of recurrence of disease (either local post induction or distal) by CT; or (c) death (see Figure 1). For patients with detected local disease at the end of the induction period, defining the EFS composite endpoint to be the date the induction treatment period ends, rather than the randomization date as suggested by a regulatory authority in the AML setting, has some very important properties. First, this definition enables rigorous and valid application of survival analysis methods in the assessment of treatment effects since such methods require it to be known whether an event has happened by any time ‘t’ simply by having information available up to that time ‘t’. Second, this definition of EFS also provides a more clinically relevant measurement of patient outcomes. For example, a patient who dies midway during the induction interval indeed should be considered to be a failure at an earlier time post randomization than a patient who survives to the end of the induction interval but does not achieve disease-free status at that time.

There are additional reasons to consider EFS as a surrogate endpoint in LAPC. LAPC is an ‘intermediate’ stage PDAC with longer OS compared with metastatic disease, with the possibility of longer tumor control using chemotherapy or radiation therapy potentially followed by surgery. Main goals of treatment in patients with LAPC are to delay local and metastatic progression, thus delaying onset of decline in QOL, specifically degree of fatigue and pain, malnutrition, parenteral nutritional support, and need for opioids for pain control, ultimately delaying death. In patients with LAPC, while the important OS endpoint would directly capture these effects on duration of survival, it may be less sensitive to the effects on enhancing the QOL. An endpoint is needed for the LAPC field that is a more directly related to the concept of DFS in adjuvant
Table 1. Definition of EFS according to studies published.

| Disease     | Resistance/failure to achieve remission | Relapse | Secondary malignancy | Death of any cause | Other                                      |
|-------------|----------------------------------------|---------|---------------------|--------------------|-------------------------------------------|
| Creutzing et al. 14 | AML                                   | X       | X                   | X                  | Early death                               |
| Langebrake et al. 15 | AML                                   | X       | X                   | X                  | X                                         |
| Marcucci et al. 16 | AML                                   | X       | X                   | X                  | X                                         |
| Rao et al. 17    | AML                                   | X       | X                   | X                  | X                                         |
| Basso et al. 18  | ALL                                    | X       | X                   | X                  | X                                         |
| Butturini et al. 19 | ALL                                   | X       | X                   | X                  | X                                         |
| Nachman et al. 20 | ALL                                    | X       | X                   | X                  | X                                         |
| Schultz et al. 21 | ALL                                    | X       | X                   | X                  | X                                         |
| Cortes et al. 22  | CML                                    | X       | Loss of complete response | X                  | Loss of cytogenetic response; discontinuation for toxicity |
| Caballero et al. 23 | CLL                                   | X and disease progression |         |         | X                                         |
| Ades et al. 24   | APL                                    | X       | X                   | X                  | X                                         |
| Devine et al. 25  | Leukemias                             | X       | X                   | X                  | X                                         |

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; CCL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; EFS, event-free survival.

setting and embraces impact of surgery following neoadjuvant therapy as well as progression and death.

While it is difficult to compare a tumor response in hematologic malignancies and solid tumors, histological complete response in LAPC may be achieved in 10–15% of cases after the administration of FOLFIRINOX chemotherapy which is increasingly used in neoadjuvant setting in LAPC in patients with good performance status. Combination of this approach and option of G/NP with surgical exploration/resection in eligible patients was recently reported in NEO LAP study. Although no differences in OS was seen between the use of FOLFIRINOX versus G/NP, the OS reported here was improved in resected versus non-resected patients. In a neoadjuvant study, the proposed novel definition of EFS may be sensitive to an intervention’s effect on the ability to achieve resection and, in turn, disease-free status at the end of induction, local relapse after surgery, and distal disease progression and death. Thus, the use of EFS would be appealing and justified in this setting.

Discussion
Previously, EFS has been used most frequently in clinical trials addressing hematological diseases such as acute leukemias. This endpoint has appealing properties in this type of severe disease setting where the early event of failure of the induction treatment is clinically very relevant.

EFS has not been cited in the DATECAN project proposing guidelines for time-to-event endpoints in trials for pancreatic cancer. This could be meaningfully influenced by the biology in the PDAC setting for which there is a consensus that a systemic therapy is required in metastatic and increasingly in neoadjuvant settings. In contrast, LAPC has properties where ‘locoregional treatments’, such as radiation therapy and surgery, have as important roles as other treatment methods such as cryoablation, high frequency focused ultrasound, irreversible electroporation, microwave/radiofrequency ablation, or photodynamic therapy.

The recent National Comprehensive Cancer Network recommendations for patients with
LAPC with good performance status include using a systemic therapy alone or followed by chemoradiation or stereotactic body radiation therapy. Hence, significant progress has been made in recent years with systematic chemotherapies of LAPC. Using a nab-paclitaxel plus gemcitabine combination, in a study by Reni et al., 77% of 177 patients had at least a 50% reduction in CA19-9 levels, and CA19-9 response was found to be an independent prognostic factor for OS. In the LAPACT study by Philip et al., serum CA19-9 concentrations decreased after six cycles of chemotherapy in most patients and 15% of them underwent curative-intent surgery. In a meta-analysis about FOLFIRINOX in LAPC by Suker et al., the authors reported a median OS of 24.2 months; in addition, 25% (9%) patients could have a surgical resection, of whom 78.4% had an R0 resection.

In LAPC, a novel endpoint is needed that would have considerable reliability in predicting the effects on OS of both neoadjuvant therapies and surgical resection. Surgery has not only a therapeutic role in LAPC, but also a diagnostic role in our proposed definition of EFS, in that it is used to assess local disease-free status at the end of induction therapy. However, to achieve sensitivity as well to the presence and the impact of microscopic distal disease, the proposed definition of EFS is based on time to detected disease, either through surgery for local disease or, in a manner analogous to ‘DFS in the adjuvant setting’, through subsequent detection of local or distal disease by CT, or to death.

While central radiology focuses on CT scan alone in detection of disease after neoadjuvant treatment, the recent results from APACT trial demonstrate the opportunities for enhanced insights by use of additional outcome measures. While CT scans are used in determination of disease free status/progression in the proposed definition of EFS, supportive endpoints could be based on insights from assessments such as CA19-9, FDG-PET, and clinical symptoms. Symptoms like pain reappearance or clinical deterioration, or increase in serum markers such as CA19-9, despite well-known limits of their sensitivity and specificity, could provide important supportive insights about disease progression.

The increasing efficacy of neoadjuvant therapies in LAPC justifies re-visiting study endpoints in order to better reflect treatment efficacy, not only accounting for effects on duration of OS, but also important potential gains in QOL for patients who have extended periods of time free of detectable disease. Thus, EFS, with the novel definition proposed in this article, should be a valuable endpoint for this clinical setting. Such an endpoint would provide important complementary insights to OS, with enhanced sensitivity and the potential to be used in the accelerated approval process for drugs in Oncology.

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References
1. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for pancreatic adenocarcinoma, https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf
2. Seufferlein T, Hammel P, Delpero JR, et al. Optimizing the management of locally advanced pancreatic cancer with a focus on induction
chemotherapy: expert opinion based on a review of current evidence. *Cancer Treat Rev* 2019; 77: 1–10.

3. Picozzi V, Alseidi A, Winter J, et al. Gemcitabine/nab-paclitaxel with pamevrumab: a novel drug combination and trial design for the treatment of locally advanced pancreatic cancer. *ESMO Open* 2020; 5: e000668.

4. Chatzizacharias NA, Tsai S, Griffin M, et al. Locally advanced pancreas cancer: staging and goals of therapy. *Surgery* 2018; 163: 1053–1062.

5. Shah R, Ostadoff KT, Kuvshinoff B, et al. Ablative therapies for locally advanced pancreatic cancer. *Pancras* 2018; 47: 6–11.

6. Brody T. *Endpoint of event free survival. Clinical trials: Study design, endpoints and biomarkers, drug safety, and FDA and ICH guidelines*. Amsterdam: Academic Press, Elsevier, 2016.

7. Kantarjian H, O’Brien S, Jabbour E, et al. Impact of treatment end point definitions on perceived differences in long-term outcome with tyrosine kinase inhibitor therapy in chronic myeloid leukemia. *J Clin Oncol* 2011; 29: 3173–3178.

8. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/efs

9. Mathoulin-Pelissier S, Gourgou-Bourgade S, Bonnetain F, et al. Survival end point reporting in randomized cancer clinical trials: a review of major journals. *J Clin Oncol* 2008; 26: 3721–3726.

10. Bonnetain F, Bonsing B, Conroy T, et al. Guidelines for time-to-event end-point definitions in trials for pancreatic cancer. *Eur J Cancer* 2014; 50: 2983–2993.

11. Othus M, van Putten W, Lowenberg B, et al. Relationship between event-free survival and overall survival in acute myeloid leukemia: a report from SWOG, HOVON/SAKK, and MRC/NCri. *Haematologica* 2016; 101: e284–e286.

12. Wudhikarn K, Bunworasate U, Julamanee J, et al. Event free survival at 24 months is a strong surrogate prognostic endpoint of peripheral T cell lymphoma. Thai Lymphoma Study Group. *Hematol Oncol* 2019; 37: 578–585.

13. Doganis D, Zborovskaya A, Trojanowski M, et al. Wilms tumour event-free and overall survival in Southern and Eastern Europe: pooled analysis of clinical data from four childhood cancer registries (1999–2017). *Eur J Cancer* 2019; 115: 37–46.

14. Creutzig U, Zimmermann M, Lehrnbecher T, et al. Less toxicity by optimizing chemotherapy, but not by addition of granulocyte colony-stimulating factor in children and adolescents with acute myeloid leukemia: results of AML-BFM 98. *J Clin Oncol* 2006; 24: 4499–4506.

15. Langebrake C, Creutzig U, Dworzak M, et al. Residual disease monitoring in childhood acute myeloid leukemia by multiparameter flow cytometry: the MRD-AML-BFM Study Group. *J Clin Oncol* 2006; 24: 3686–3692.

16. Marcucci G, Maharry K, Whitman SP, et al. High expression levels of the ETS-related gene, ERG, predict adverse outcome and improve molecular risk-based classification of cytogenetically normal acute myeloid leukemia: a Cancer and Leukemia Group B Study. *J Clin Oncol* 2007; 25: 3337–3343.

17. Rao AV, Valk PJ, Metzeler KH, et al. Age-specific differences in oncogenic pathway dysregulation and anthracycline sensitivity in patients with acute myeloid leukemia. *J Clin Oncol* 2009; 27: 5580–5586.

18. Basso G, Veltroni M, Valsecchi MG, et al. Risk of relapse of childhood acute lymphoblastic leukemia is predicted by flow cytometric measurement of residual disease on day 15 bone marrow. *J Clin Oncol* 2009; 27: 5168–5174.

19. Butturini AM, Dorey FJ, Lange BJ, et al. Obesity and outcome in pediatric acute lymphoblastic leukemia. *J Clin Oncol* 2007; 25: 2063–2069.

20. Nachman JB, La MK, Hunger SP, et al. Young adults with acute lymphoblastic leukemia have an excellent outcome with chemotherapy alone and benefit from intensive postinduction treatment: a report from the children’s oncology group. *J Clin Oncol* 2009; 27: 5189–5194.

21. Schultz KR, Bowman WP, Aledo A, et al. Improved early event-free survival with imatinib in Philadelphia chromosome-positive acute lymphoblastic leukemia: a children’s oncology group study. *J Clin Oncol* 2009; 27: 5175–5181.

22. Cortes JE, Jones D, O’Brien S, et al. Results of dasatinib therapy in patients with early chronic-phase chronic myeloid leukemia. *J Clin Oncol* 2010; 28: 398–404.

23. Caballero D, Garcia-Marco JA, Martino R, et al. Allogeneic transplant with reduced intensity conditioning regimens may overcome the poor prognosis of B-cell chronic lymphocytic leukemia with unmutated immunoglobulin variable heavy-chain gene and chromosomal abnormalities (11q- and 17p-). *Clin Cancer Res* 2005; 11: 7757–7763.

24. Adès L, Chevret S, Raffoux E, et al. Is cytarabine useful in the treatment of acute promyelocytic leukemia? Results of a randomized trial from the European Acute Promyelocytic Leukemia Group. *J Clin Oncol* 2006; 24: 5703–5710.
25. Devine S, Dagher RN, Weiss KD, et al. Good clinical practice and the conduct of clinical studies in pediatric oncology. *Pediatr Clin North Am* 2008; 55: 187–209.

26. Fleming TR and Harrington DP. *Counting processes and survival analysis*. Chichester: Wiley, 1991.

27. Pietrasz D, Turrini O, Vendrely V, et al. How does chemoradiotherapy following induction FOLFIRINOX improve the results in resected borderline or locally advanced pancreatic adenocarcinoma? An AGEO-FRENCH multicentric cohort. *Ann Surg Oncol* 2019; 26: 109–117.

28. Kunzmann V, Algül H, Goekkurt E, et al. Conversion rate in locally advanced pancreatic cancer (LAPC) after nab-paclitaxel/gemcitabine- or FOLFIRINOX-based induction chemotherapy (NEOLAP): final results of a multicenter randomised phase II AIO trial. *Ann Oncol* 2019; 30: v253–v324.

29. Huguet F, Goodman KA, Azria D, et al. Radiotherapy technical considerations in the management of locally advanced pancreatic cancer: American-French consensus recommendations. *Int J Radiat Oncol Biol Phys* 2012; 83: 1355–1364.

30. Reni M, Zanon S, Balzano G, et al. Selecting patients for resection after primary chemotherapy for non-metastatic pancreatic adenocarcinoma. *Ann Oncol* 2017; 28: 2786–2792.

31. Philip AP, Lacy J, Portales F, et al. Nab-paclitaxel plus gemcitabine in patients with locally advanced pancreatic cancer (LAPACT): a multicentre, open-label phase 2 study. *Lancet Gastroenterol Hepatol* 2020; 5: 285–294.

32. Suker M, Beumer BR, Sadot E, et al. A patient-level meta-analysis of FOLFIRINOX for locally advanced pancreatic cancer. *Lancet Oncol* 2016; 17: 801–810.