Editorial Commentary

A nomogram for predicting survival of patients with locally advanced pancreatic cancer treated with chemoradiotherapy: an editorial comment

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Introduction

Pancreatic cancer remains one of the most aggressive malignancies which has a mortality nearly parallel to incidence. In the United States, for example, statistics from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program estimates 55,440 new cases of pancreatic cancer in the U.S. in 2018, with 44,330 estimated deaths (1). Based on data collected from 2008–2014, only 8.5% of patients survive 5 years or longer (1). It is widely held that a combination of surgical resection and systemic chemotherapy provides the optimal treatment for pancreatic cancer. Unfortunately, only about 15–20% of patients present with resectable disease.

Surgical resectability previously had taken presence of metastatic disease or vascular involvement into consideration. Anatomic vascular involvement was classified into groupings based on vascular involvement, from abutment <180° to encasement. A 2017 international consensus also reported biologic factors that should be considered in the definition of borderline-resectable pancreatic cancer (2). Serum CA 19-9 of >500 IU/mL and/or positive regional lymph node metastases based on biopsy or PET-CT scan was added to the anatomic definition, as was a conditional definition of poor performance status, with PS of 2 or greater (2). National cancer care guidelines, including the U.S. NCCN guidelines and European Society of Medical Oncology, both suggest inclusion in clinical trials if possible, for patients with borderline resectable or locally advanced disease. If not treated within the context of a clinical trial, both suggest a trial of chemotherapy and potential radiation to improve margin-negative resection (3,4); however, this is not supported by high-level trials. Because it is unknown what the optimal treatment sequence and strategy should be, ongoing investigation is being performed looking at predictive models.

Discussion

Choi *et al.* have recently created a nomogram for prediction of overall survival in patients with locally advanced pancreatic cancer treated with chemoradiotherapy (5). In this study, the authors evaluated 426 patients with borderline resectable or locally advanced pancreatic cancer who underwent chemoradiotherapy between 1/2004 and 12/2015 and had pre-treatment PET/CT scans and CA19-9 levels. Univariate analysis demonstrated surgical resection, pre-treatment SUVmax <3.5, SUV decline rate ≥60%, pre-treatment CA 19-9 ≤400 U/mL, post-treatment CA 19-9 ≤100 U/mL, and a CA 19-9 decline rate >40% were independently significant for predicting improved progression free survival. In consideration of overall survival, a total radiation dose ≥61 Gy and IMRT was also significant in addition to the previously mentioned factors. In multivariate analysis, however, surgical resection, pre-treatment SUVmax <3.5 and pre-treatment CA 19-9 ≤400 U/mL are the only factors predictive of both overall and progression-free survival. Radiation dose ≥61 Gy was also

predictive of improved overall survival (5). Based on these data, a nomogram was constructed including the variables high RT dose ≥61 Gy, surgical resection, pre-treatment SUV <3.5, and pre-treatment CA 19-9 ≤400 U/mL. Three groups were stratified based on accumulated points: low-risk, intermediate-risk, and high-risk, with significantly different overall survival based on grouping. The authors propose that this nomogram would be helpful for patient consultation and treatment decision-making in clinical practice (5).

The authors should be commended on compiling a nomogram from a robust dataset; however, the utilization of the nomogram may not be widely applicable, and several factors must be considered. Firstly, there is a marked difference in patients with borderline resectable *vs*. locally advanced pancreatic cancer. Resection rates are higher in borderline resectable pancreatic cancer patients *vs*. locally advanced patients following neoadjuvant chemoradiation, typically with a gemcitabine or 5-fluorouracil based regimen (6). It is unclear if combining the two groups of borderline resectable and locally advanced pancreatic cancer patients impacts the nomogram predictive model than if each group was considered in isolation. Secondly, another metric that is significant in the nomogram is high-dose radiation, of 61 Gy. Most recommendations for neoadjuvant chemoradiation, including recommendations of the NCCN, are for doses of 45–54 Gy. Doses higher than 54 Gy could be considered in the context of a clinical trial (4). Conventional doses of radiation do not seem to significantly affect survival based on the authors' dataset, and it is unclear why patients received such high doses of radiation.

Another factor to consider is the time frame of the nomograph dataset, which spans from 1/2004–12/2015; this may explain why 50% received gemcitabine-based concurrent chemotherapy. The other 50% received an unspecified regimen. Since 2011, two regimens have been approved as first-line chemotherapy for pancreatic cancer, applied to both borderline resectable and locally advanced patients: gemcitabine in combination with nab-paclitaxel and FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan and oxaliplatin) (7). These regimens have had more success in treating patients compared with gemcitabine-alone, so it is unknown whether these regimens have a greater impact and thus survival in the later data set years. Parsing out chemotherapy regimens may help understand the true impact of specific chemotherapy regimens, rather than broadly considering chemotherapy as a variable.

Surgical resection remains one of the mainstays of therapy and improved survival. With respect to borderline resectable and locally advanced patients, resection feasibility is often dependent upon not only the response to neoadjuvant chemoradiation but also the surgical treatment team and their experience with vascular reconstruction. Although all of the study patients were treated at a single institution, it is unknown how many patients required concomitant vascular reconstruction and how many achieved a R0 resection.

One of the unique aspects of this study is the inclusion of biologic factors, including pre-treatment CA19-9, pre-treatment SUV value and SUV change with treatment, although ultimately the SUV change was not found to be predictive of overall survival. Many studies have also suggested that an elevated CA19-9 is suggestive of worse prognosis and potentially micrometastatic disease (2). Interestingly, the SUV change was not found to predict survival; perhaps other criteria, such as RECIST radiographic criteria, would also be useful. Thus, while the inclusion of biologic factors is important, it is still unclear how they should be utilized as the patient progresses through neoadjuvant treatment.

Conclusions

In conclusion, this current nomogram incorporates many factors already determined to be predictive of aggressive disease, including elevated CA19-9 and PET-avid disease. The nomogram incorporates high-dose radiation, which is uncommonly utilized; therefore, it is unclear if this nomogram should be utilized, since this would be an uncommon factor to consider. It is commendable that the authors have produced a model that may assist clinical decision-making; however, it is unclear if this truly would impact patient care. For instance, would a patient with a high-risk nomogram but resectable disease anatomically not be recommended to undergo resection? Clearly, further investigation is required, evaluating various situations to determine best practice.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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