Pattern, timing, and predictors of recurrence following pancreatectomy for pancreatic ductal adenocarcinoma: how do they matter?

Charing C. N. Chong

Department of Surgery, Prince of Wales Hospital, Chinese University of Hong Kong, Hong Kong, China

Correspondence to: Charing C. N. Chong. Department of Surgery, 4/F, Lui Che Woo Clinical Sciences Building, Prince of Wales Hospital, Shatin, N.T., Hong Kong, China. Email: chongcn@surgery.cuhk.edu.hk.

Provenance: This is an invited Editorial commissioned by Dr. Jin He (Department of Surgery, The Johns Hopkins Hospital, Baltimore, MD, USA).

Comment on: Groot VP, Rezaee N, Wu W, *et al.* Patterns, timing, and predictors of recurrence following pancreatectomy for pancreatic ductal adenocarcinoma. Ann Surg 2018;267:936-45.

Received: 15 April 2018; Accepted: 07 May 2018; Published: 18 May 2018.

doi: 10.21037/jovs.2018.05.14

View this article at: http://dx.doi.org/10.21037/jovs.2018.05.14

Pancreatic ductal adenocarcinoma (PDAC) remains one of the deadliest malignancies, not only in the United States, but also worldwide. And its incidence is rising. The prognosis is usually grave even after curative resection. A better understanding on the characters of recurrence is necessary. In the article "*Pattern*, *timing*, *and predictors of recurrence following pancreatectomy for pancreatic ductal adenocarcinoma*", Groot *et al*. identified unique recurrence-free survival (RFS) curves for specific recurrence patterns and specific recurrence locations were correlated with distinctive clinicopathological factors (1). It is a large and single institutional study and is excellent with respect to retrospective analysis on this topic. These findings are indicated of biologic heterogeneity of PDAC. This is especially important in the era of personalized medicine.

The study cohort consisted of 692 patients who had undergone upfront pancreaticoduodenectomy or total pancreatectomy over a 10-year period from a center with an excellent track record on pancreatectomy. The study population was homogenous. The authors clearly defined the study population and outcome measures. They set very clear and detailed inclusion and exclusion criteria and selected a homogenous group of patients for further analysis. Nevertheless, they could still obtain a very respectful sample size. It could only be done in such a high-volume center. This homogenous study population from a mono-institution eliminated the variability from surgical and pathological assessment, which is particularly important when interpreting the factors associated with recurrence. The prospectively maintained database also played an important role in the accurate analysis of clinicopathological features associated with the site of first recurrence. The authors had characterized the pattern and timing of disease recurrence following resection of PDAC and identified distinctive clinicopathological features and RFS curves for different recurrence pattern. Since the analyses was made from a very clean and clear database, the authors can make the hypothesis that unique biological difference exist among PDAC. It opens the door to future genetic or molecular studies.

The 2-year recurrence rate of this cohort was 76.7% and most patients first recurred at isolated distant sites (57.8%). The high early recurrence rate, once again, leads to the issue of adjuvant or neoadjuvant therapy in PDAC. From their own data, median RFS for patients receiving adjuvant chemoradiotherapy or chemotherapy was significantly longer when compared with patients who did not received any adjuvant treatment. Both chemotherapy and chemoradiotherapy were found to significantly reduce the likelihood of local and distant recurrence. These findings echoed with the current literatures and clinical practice. Results from three clinical trials (CONKO-1, ESPAC-3, and ESPAC-4) had shown that adjuvant chemotherapy after surgery may improve survival (2-4). The American Society of Clinical Oncology guideline recommends 6 months of adjuvant chemotherapy to all

patients with resected pancreatic cancer who did not receive preoperative therapy and in the absence of medical or surgical contraindications (5). However, as the authors had mentioned, data on the regimen, doses, and frequency of adjuvant therapy were missing in this study. Therefore, other potential associations could not be appreciated by this study. These information are important especially when they talked about tumour biology, genetic and molecular study. Current treatment schemes that have demonstrated efficacy include gemcitabine alone, 5-fluorouracil, or the combination of gemcitabine and capecitabine for 6 months (6).

Apart from that, results from this paper may add some insights on the role of radiotherapy in the adjuvant treatment. Multivariate analysis in this paper revealed that only patients who received adjuvant chemoradiotherapy, but not adjuvant chemotherapy alone, had a significantly decreased likelihood of local-only recurrence (HR =0.64, P=0.024) when compared with patients who did not receive adjuvant therapy. Hence, the authors concluded that adjuvant radiation therapy played an important role in preventing local recurrence, especially in patients with a positive resection margin. However, their analysis included 451 (65.2%) and 241 (34.8%) of patients received R0 and R1 resection respectively. In order to evaluate the effect of adjuvant radiotherapy, separate analyses on patients received R0 and R1 resection may be necessary. Despite a number of phase II trials had analyzed the role of radiotherapy in adjuvant settings, the results were contradictory. To date, there exists important difference in the adjuvant management of PDAC between Europe (adjuvant chemotherapy alone) and the United States (adjuvant chemoradiotherapy). Liao *et al*. conducted a meta-analysis and concluded that chemotherapy alone reduced mortality after pancreatectomy and chemoradiotherapy followed by chemotherapy was less effective in prolonging overall survival but more toxic compared chemotherapy alone (7). Currently, adjuvant radiotherapy is recommended in patients with R1–R2 resection or in selected cases with node positive disease (5,6).

Groot *et al*., in this paper, also identified that most patient first recurred at isolated distant sites (57.8%) and liver was the most common site. And the proportion of recurrence locations differed significantly at progressive time points. At 6 months, liver-only recurrence was responsible for almost half of all documented recurrence (47.6%). On the other hand, liver-only recurrence accounted for only 12.1% of the recurrence occurring after 48 months (P<0.001). The prevalence of liver recurrence diminishes over time. These results suggested that micrometastases might already exist in the liver at the time of surgery. Nowadays, endoscopic retrograde cholangiopancreatography (ERCP) is the most commonly used method for pre-operative biliary drainage, if that was being done. Whether the retrograde manipulation may introduce tumour seeding in liver would be an interesting question to investigate. I wonder if the authors have the data to analysis this aspect.

One of the most outstanding of this paper is the identification of distinctive clinicopathological features correlated with different patterns of recurrence. Nevertheless, lymph node ratio (LNR) >2.0 was a strong predictor for all distant metastasis. LNR was defined as the number of positive lymph nodes divided by the number of total nodes harvested which means that both the number of positive lymph nodes and the number of total nodes harvested or examined are essential determinants of LNR. The value and extend of lymphadenectomy has been extensively investigated. Elshaer *et al.* conducted a systematic review of the prognostic value of LNR, number of positive nodes and total nodes examined in PDAC. They found that LNR and number of positive nodes, but not the total nodes examined, were poor predictors for overall survival (8). Having said that, N0 patients who have fewer than 12 lymph nodes examined might be understaged according to a previous paper from the authors' institution (9). It is hoped that this message become more widely disseminated, not only among surgeons, but also to the pathologists.

In conclusion, this research advanced the knowledge on the pattern and timing of disease recurrence after pancreatectomy for PDAC. The findings of distinct RFS curves and different predictors for specific recurrence pattern had shed some lights on the role of adjuvant therapy, LNR, as well as molecular study in PDAC. I read this article with great interest and it is hoped that the messages from this study can be widely disseminated to professions involved in the management of PDAC.

Acknowledgements

None.

Footnote

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

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doi: 10.21037/jovs.2018.05.14
Cite this article as: Chong CC. Pattern, timing, and predictors of recurrence following pancreatectomy for pancreatic ductal adenocarcinoma: how do they matter? J Vis Surg 2018;4:106.