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Response ''Surgeon Age in Relation to Prognosis After Esophageal Cancer Resection''

Reply:

We would like to thank you for the opportunity to respond to the letter by Lu et al that commented on our recent publication entitled, ''Surgeon Age in Relation to Prognosis after Esophageal Cancer Resection.''[1] Through using the highly sensitive statistical methodology of Risk-Adjusted Cumulative Sum curve (RA-CUSUM) analysis, the study showed that surgeon ages $\leq$51 and $\geq$56 years were associated with increases in 90-day and 5-year mortality compared within surgeon age between 52 and 55 years. All the points raised by Lu et al have been addressed within the design of the study or by previous publications from the research group using this dataset.

Firstly, Lu et al state that ''it was unclear whether there is a relationship between hospital volume and postsurgical mortality in the study.'' As cited in the introduction of this manuscript, our research group has previously published from this dataset to identify the greater importance of surgeon volume over hospital volume in determining long-term prognosis from esophageal cancer surgery.[2] That study showed no association between hospital volume and mortality after adjustment for surgeon volume, whereas the association between surgeon volume and mortality remained after adjustment for hospital volume (and other covariates).

Secondly, Lu et al state that ''surgeon volume has been less emphasized in this study.'' As stated in the methods section of the analysis, ''Potential confounding factors (surgeon volume and year of surgery) with a strong correlation with the exposure (surgeon age) were not included in this risk adjustment, which is standardized methodology for RA-CUSUM. However, given the clinical importance of distinguishing surgeon volume and year of surgery from surgeon age, they were included in the subsequent Cox regression analyses.'' Therefore, as stated in Table 2, surgeon volume was adjusted for in the analyses, which demonstrate the significant increases in 90-day and 5-year mortality with surgeon ages $\leq$51 and $\geq$56 years compared with surgeon age 52 to 55 years.

Lu et al also state that ''the influence of surgeon specialization on the prognosis of esophageal cancer, this study did not give further illustration.'' The study period started in 1987 when esophageal cancer specialization had not taken place within Sweden. However, surgeon volume may be considered as a surrogate for esophagectomy experience or specialization, and as stated above, this was adjusted for in the analyses presented in Table 2.

Finally, Lu et al state that ''this analysis failed to adjust for surgical complexity.'' As stated in the methods section, ''Potential confounding factors included in the models were age (continuous variable), sex (male or female), comorbidity (Charlson comorbidity score 0, 1 or $\geq$2), pathological tumor stage (0 or I, II, III or IV), tumor histology (adenocarcinoma or squamous cell carcinoma), and use of neoadjuvant therapy (yes or no).'' In a national dataset such as this, reflecting surgical complexity is challenging; however, with adjustment for patient physiological status and tumor stage, histology, and neoadjuvant therapy, the adjustment is adequate to reflect complexity of surgical cases within the dataset.

We again thank Lu et al for their interest in this study.

The authors declare there are no conflicts of interest.

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Prevention of Clinically-relevant Postoperative Pancreatic Fistula After Pancreticoduodenectomy

To the Editor:

We read with interest the recent article by Ecker et al[1] that aimed to characterize patients with a high fistula risk score (FRS), from 7 to 10, and to investigate the efficacy of various mitigation strategies for clinically-relevant postoperative pancreatic fistula (CR-POPF) after pancreaticoduodenectomy (PD). The authors concluded that risk mitigation was optimized by using externalized stents and omitting prophylactic octreotide—a solution that significantly reduced the CR-POPF rate (12.2% vs. 33.5%. $P < 0.001$).

Though very interesting, this paper suffers from some important biases.

First of all patient selection is not reported in detail. The study deals with 5323 PDs performed at 17 internationally-acknowledged institutions, including the International Study Group on Pancreatic Fistula (ISGPF), from January 2003 to July 2016. According to data already published in the English literature by the participating authors (*J Gastrointest Surg*. 2016;20:2052–2062; *Am J Surg*. 2017;214:450–455; *Ann Surg*. 2017 Dec 12. doi: 10.1097/SLA.0000000000002614. [Epub ahead of print]; *HPB (Oxford)*. 2017;19:264–269; *Surgery*. 2014;156:939–46; *J Gastrointest Surg*. 2012;16:275–281; *Br J Surg*. 2016; 103:553–563; *Ann Surg Oncol*. 2010;17: 991–997; *J Gastrointest Surg*. 2014;18:1760–1769; *World J Gastrointest Surg*. 2017;9:73–81; *Am J Surg*. 2016;212:195–201; *Abdom Radiol (NY)*. 2017 Aug 21. doi: 10.1007/s00261–017–1290–5. [Epub ahead of print]; *J Surg Res*. 2018;221:43–48; *Am J Surg*. 2015;209:1053–1062), the estimated number of PDs performed by the 17 institutions during the same period was well over 10,500. A large number of PDs were therefore excluded from the study either by the participating institutions or by the center performing the statistical analysis. The authors stated that cases were excluded "if any of the 4 elements of the FRS were unavailable," and that small proportions (<20%) of early cases seen at some institutions were excluded for this reason. The exact number of PDs excluded due to missing FRS data was not reported, however.

A second bias concerns the exclusion from the analysis of 4801 patients with a negligible, low, or moderate FRS (5323 minus 522 patients with a high FRS patients included in the analysis). Unfortunately, the exact number of PDs included in each of these risk score cohorts was not reported.[1] Based on another paper by the same authors,[2] however, the same 17 international institutions performed 5.316 PDs during the same period (January 2003 to July 2016) in patients distributed by FRS as follows: 433 negligible risk, 1200 low risk, 3125 moderate risk, and 558 high risk. This last group was considerably more numerous than the 522 patients with a high FRS discussed by Ecker et al.[1] Judging from the incidence of CR-POPFs among the patients with a negligible, low, or moderate FRS[1] and the distribution of the patients by FRS,[2] we can estimate that between 659 and 669 (12.4% to 12.6%) of the 5323 patients developed a CR-POPF. Testing the efficacy of the proposed mitigation strategy in preventing CR-POPFs on the readily-available cohort of 4801 patients (and about 557–567 CR-POPFs, ie, 659–669 minus the152 CR-POPFs included in the analysis) would have been very useful to readers of the paper.

A third bias concerns the authors' failure to report the mortality rate due to CR-POPFs. Judging from a review of the English literature published between 1990 and 2015,[3] the reported mortality rate associated with Grade C POPFs is extremely variable (from 0% to 100%). This means that reducing the incidence of CR-POPFs does not necessarily coincide with a lower POPF-related mortality rate. The POPF-related mortality rate was also rarely reported in prospective randomized studies, as this information was provided in only 3 of the 25 randomized controlled trials concerning 608 out of a total of 2.754 patients considered in the 10 systematic reviews and meta-analyses that compared internal and external stents.[3] A further contribution from Ecker et al[1] on the efficacy of various mitigation strategies in preventing CR-POPF-related mortality would therefore have been very important.

Last but not the least the authors[1] did not consider another possible mitigation strategy, the use of venting stents to reduce the incidence of CR-POPFs and the POPF-related mortality rate after PD.[3,4] According to one review,[3] using externally venting stents coincided with a lower POPF-related mortality rate (0.3%) than using externalized pancreatic stents (0.5%). The use of externalized pancreatic stents was the only mitigation procedure significantly associated (in 4762 patients; $P = 0.014$) with a lower POPF-related mortality rate by comparison with patients without stents (21,856). Unfortunately, venting stents were used in only 312 patients retrieved from the English literature so the difference failed to reach statistical significance.

When Oguro et al[4] used a combination of externalized pancreatic stents and externally venting stents, they obtained a CR-POPF rate of 9%, a Grade C POPF rate of 1.1%, and a zero mortality rate among 386 consecutive patients.

The POPF-related mortality rate has remained at approximately 1% over the past 25 years.[3] Any contribution to the identification of efficient mitigation strategies to reduce this rate would be welcome. Clarifying the above-mentioned issues would give us a better idea of how to reduce the CR-POPF rate and the POPF-related mortality rate after PD, as well as facilitating the design of further prospective randomized controlled trials.

The authors report no conflicts of interest.

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Response to: Managing the High-risk Pancreatic Anastomosis

Reply:

We thank Drs. Pedrazzoli and Sperti for their critical insights into our recently published manuscript on optimizing fistula mitigation strategies for high-risk scenarios of pancreatoduodenectomy (PD).[1] They raise several questions that we hope to address in order.

First, we agree that it would be a considerable source of bias if more than half of all PDs performed by the participating institutions were excluded. Given the high annual PD volume of each of the 17 institutions and the long study period (2003–2016), it would certainly be expected that many more than the 5323 PDs included in the analysis would have been available. However, 2003 and 2016 are the "general boundaries" of the study period, and the exact times of inclusion varied among institutions (ie, some throughout the duration, others for discreet portions). Still, each institution contributed all consecutive cases during the time period they contributed, and the rate of excluded patients because of unknown fistula risk score (FRS) variables was <20% relative to each (institution-specific) inclusion timeframe. In most cases, this exclusion cohort was far less than 20%. We would, however, also caution at assuming study volume through piecing together a quilt-work of studies published in the literature by participating institutions over time, as such accounting can be inaccurate in other ways.