Letter to the Editor

What Hides Beyond the Numbers: Statistics or Real Practice?

Re: Stolzfus KC, Shen B, Tchelebi L, et al. Impact of facility surgical volume on survival in patients with cancer. J Natl Compr Canc Netw 2021; 19(5):495–503.

We warmly congratulate Stoltzfus et al[1] on their excellent article, "Impact of Facility Surgical Volume on Survival in Patients With Cancer," published in the May 2021 issue of *JNCCN*. This is a pioneer great effort to evaluate the impact of surgical volume on survival in patients with cancer. The statistics convince that patients treated surgically at high-volume centers have higher survival rates. As a part of conclusions, the authors firmly state that patients with pancreatic and esophageal cancer should be referred to high-volume centers.

However, thoughtful reading raises a few questions. First, what are the real numbers behind the presented statistics? During the early years of the study, up to 60% of cases were excluded due to unknown clinical staging. All patients who received neoadjuvant chemoradiotherapy were also excluded.[1] Furthermore, inaccurate clinical staging can result in both undertreatment and overtreatment of patients.[2] In our opinion, inclusion of patients with 0–I disease may also cause deviation of the results and influence conclusions.

Another limitation is the classification of hospital volume based on total surgical volume rather than procedure-specific volume. Additionally, no data on procedure-related surgical complications are provided. The registry included tumor characteristics, but data regarding treatments are missing. Awareness of these findings is crucial when research and decision-making is based on a registry.[3]

The comparison of patient data during 2004 through 2013 may also affect results, given that oncologic treatment changed rapidly during these years with new biologic and immunologic therapies, which were likely available mainly in high-volume centers, mostly in the early period. Then, enrollment of patients in clinical trials and the availability of innovative technologies (eg, FDG-PET, molecular sequencing) was also a "privilege" of such centers.

Further investigation of the most impactful factors on survival is needed. Several studies have shown that surgeon volume, rather than hospital volume, is an important factor.[4] Another study supported the evidence that lower-volume hospitals with excellent resources have similar results as high-volume centers.[5] Furthermore, in a large study evaluating the impact of volume on pancreatic cancer results, despite its conclusion, found differences only when comparing hospitals with as little as 5 versus 50 cases annually.[6] The opening of new surgical units and the subsequent relocation of personnel is common, and therefore it remains unclear whether the moving of experienced staff to lower-volume hospitals will affect the results.

We greatly appreciate the article by Stoltzfus et al,[1] but believe that the authors' strong conclusions are somewhat premature. A stratified prospective data collection is strongly needed.

Boris Kessel, MD[a,†]*; Maya Paran, MD*[a]*; and Katerina Shulman, MD*[b]

[a]*Division of General Surgery, Hillel Yaffe Medical Center, and* [b]*Oncology Department, Carmel Hospital, Technion, Haifa, Israel*

[†]*Email: bkkessel01@gmail.com*

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References

1. Stolzfus KC, Shen B, Tchelebi L, et al. Impact of facility surgical volume on survival in patients with cancer. J Natl Compr Canc Netw 2021;19: 495–503.
2. Burneikis D, Lavryk O, Gorgun E, et al. Clinical staging accuracy and the use of neoadjuvant chemoradiotherapy for cT3N0 rectal cancer: Propensity score matched National Cancer Database analysis. Am J Surg 2021;221: 561–565.
3. Lunkka P, Malila N, Ryynänen H, et al. Accuracy of Finnish Cancer Registry colorectal cancer data: a comparison between registry data and clinical records. Scand J Gastroenterol 2021; 56:247–251.
4. Schmidt CM, Turrini O, Parikh P, et al. Effect of hospital volume, surgeon experience, and surgeon volume on patient outcomes after pancreaticoduodenectomy: a single-institution experience. Arch Surg 2010;145:634–640.
5. Joseph B, Morton JM, Hernandez-Boussard T, et al. Relationship between hospital volume, system clinical resources, and mortality in pancreatic resection. J Am Coll Surg 2009;208: 520–527.
6. Toomey PG, Teta AF, Patel KD, et al. High-volume surgeons vs high-volume hospitals: are best outcomes more due to who or where? Am J Surg 2016;211:59–63.

Authors' Reply

To the Letter to the Editor by Kessel et al

We thank Kessel et al for their letter regarding our article published in the May 2021 issue of *JNCCN*,[1] and thank the editors for the opportunity to respond. Kessel et al present 3 concerns. First, they perceive that up to 60% of patients with "unknown" clinical staging were excluded from the analysis, and that patients with neoadjuvant chemoradiotherapy were excluded. Exclusion of these patients would limit the implications of the results. They believe inclusion of patients with stage 0–I disease also influences the conclusion. Second, they believe that the use of facility total surgical volume is limited, and that procedure-specific or provider-specific volume would be better, along with procedure-related complications. Third, they believe that comparison of data across the study period (2004–2013) is limited due to advancement of available treatment options, including novel systemic therapies. In this response letter, we clarify these points and address their concerns.

First, our team performed the survival analysis with all patients as well as with only those with complete information on stage and found essentially the same results. A total of 32.5% of patients had unknown stage (Table 1 in our article), and this may be because in the National Cancer Database (NCDB) there are separate variables for TNM stages and for "overall" clinical stage, based on TNM values. TNM stage information is available for most everyone, whereas overall stage is not always available due to evolution of the database and limitations with the NCDB,[2] as discussed in our article. There were

<10% of patients with stage 0 disease, and >70% of these were women with breast cancer (ductal carcinoma in situ, which is expected). Similarly, patients who received neoadjuvant chemoradiotherapy were also included (shown in Table 1 in our article). Our group has written a separate article on the effects of facility radiotherapy volume on survival.[3]

Second, in reference to the comment regarding total surgical volume versus procedure-specific volume, we agree with Kessel et al's statement that this is a limitation of the NCDB and of our findings. Information about surgeon volume and procedure-related surgical complications is unavailable.[2] Additional analyses utilizing such data, when available, would be a great complement to the present study. However, there are also advantages to evaluating facility volume: (1) at consultation, patients may see several equally competent physicians from the same practice, and they would not necessarily know which physician(s) will be involved in the procedure; (2) sometimes multiple physicians are involved in the case; and (3) parsing the data out to individual providers will preclude most of the other analyses, given that the number of surgeries from more rare cancers is already limited. Figure 1 in our article shows limited numbers for many practices performing surgeries on the brain, pancreas, and esophagus. Overall facility surgical volume may be a better composite quality metric that is a surrogate for other quality metrics, such as availability of clinical trials[4] or presence of cardio-oncology clinics,[5,6] which may also improve survival.

Third, although cancer care has improved over the past decades, the impact of novel cancer treatments via biologic or immune agents did not have significant changes from 2004 to 2013, and likely had limited impact on survival for the patients in this analysis. For all cancers, immunotherapy was used in <4% of the patient populations during the study period (range, 0.03%–3.25%), and most of these were agents such as IL-2 for kidney cancer. Additionally, approximately 13% of patients received Bacillus Calmette-Guérin (coded as a type of immune therapy) for bladder cancer. Checkpoint inhibitor immunotherapy (with anti–PD-1, anti–PD-L1, or anti–CTLA-4 agents) was not available in the market until about 2014. Moreover, the percentage of patients estimated to respond to checkpoint inhibitor drugs was 0.14% in 2011 and increased to 12.46% in 2018 (a relatively small percentage).[7] Similarly, for genome-informed treatment, in 2006 the percentage estimated to benefit was 1.31% (95% CI, 1.28%–1.34%), and in 2018 it had increased to 6.62% (95% CI, 6.56%–6.68%).[8] In a meta-analysis of clinical trials, the addition of tyrosine kinase inhibitors to definitive radiotherapy did not improve overall survival (hazard ratio, 1.02; 95% CI, 0.90–1.15; P=.76) but did increase toxicity (relative risk, 1.18; 95% CI, 1.06–1.33; P=.009).[9] Thus, we doubt these drugs had substantial effect.

In conclusion, our study provides a valuable contribution to the scientific literature on the impact of facility surgical volume on survival. Additional analyses were conducted to ensure our results were presented in the most appropriate manner; however, we recognize there are some limitations to the data that are out of our control. We have performed additional studies to expand on these findings, some of which highlight the concerns presented by Kessel et al. We are grateful to the authors' attention to our findings and appreciate the opportunity to respond.

Kelsey C. Stoltzfus, MPH[a];
Biyi Shen, MS[b];
Leila Tchelebi, MD[a];
Daniel M. Trifiletti, MD[c];
Niraj J. Gusani, MD[b,d];
Vonn Walter, PhD[b];
Ming Wang, PhD[b]; and
Nicholas G. Zaorsky, MD, MS[a,b,†]

[a]Penn State Cancer Institute, Hershey, Pennsylvania;
[b]Penn State College of Medicine, Hershey, Pennsylvania;
[c]Mayo Clinic, Jacksonville, Florida; and
[d]Baptist MD Anderson Cancer Center, Jacksonville, Florida

[†]Email: nicholaszaorsky@gmail.com; nzaorsky@pennstatehealth.psu.edu

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References

1. Stoltzfus KC, Shen B, Tchelebi L, et al. Impact of facility surgical volume on survival in patients with cancer. J Natl Compr Canc Netw 2021;19:495–503.
2. Boffa DJ, Rosen JE, Mallin K, et al. Using the National Cancer Database for outcomes research: a review. JAMA Oncol 2017;3:1722–1728.
3. Tchelebi LT, Shin B, Wang M, et al. Impact of radiation therapy facility volume on survival in patients with cancer. Cancer, in press.
4. Zaorsky NG, Zhang Y, Walter V, et al. Clinical trial accrual at initial course of therapy for cancer and its impact on survival. J Natl Compr Canc Netw 2019;17:1309–1316.
5. Stoltzfus KC, Zhang Y, Sturgeon K, et al. Fatal heart disease among cancer patients. Nat Commun 2020;11:2011.
6. Zaorsky NG, Zhang Y, Tchelebi LT, et al. Stroke among cancer patients. Nat Commun 2019; 10:5172.
7. Haslam A, Prasad V. Estimation of the percentage of US patients with cancer who are eligible for and respond to checkpoint inhibitor immunotherapy drugs. JAMA Netw Open 2019;2:e192535.
8. Marquart J, Chen EY, Prasad V. Estimation of the percentage of US patients with cancer who benefit from genome-driven oncology. JAMA Oncol 2018;4:1093–1098.
9. Tchelebi L, Batchelder E, Wang M, et al. Radiotherapy and receptor tyrosine kinase inhibition for solid cancers (ROCKIT): a meta-analysis of 13 studies JNCI Cancer Spectrum 2021:pkab050.