

# Letters

## COMMENT & RESPONSE

### Early Surgery for Painful Chronic Pancreatitis

**To the Editor** We appreciate the authors' attempt to publish the long-term follow-up of the ESCAPE randomized clinical trial.<sup>1</sup> We also appreciate the candor with which they acknowledged the limitations of the study—namely, nonstandardized follow-up, the retrospective nature of the analysis, only a single-point data collection, and nonstandardized use of interventions during follow-up.<sup>2</sup> While the authors themselves warrant caution in interpreting the results given these limitations, they concurrently conclude that the results strengthen the recommendation for early surgery and dwindle the role of endotherapy.

The intent of this letter is not to debate whether surgery first or endotherapy first is better, but instead to express a few additional concerns that preclude the strong claim that early surgery is the way to go while the endotherapy-first option has no role.

First, the effect size of the long-term impact of early surgery was not reported in the article. Effect size would have been a stronger and more clinically relevant statistic compared to the *P* value.

Second, the sample size of the original ESCAPE trial was 88 participants, which was adjusted to account for 10% loss to follow-up. In the present study, 2 patients refused consent and 25 were lost of follow-up, thereby excluding 27 patients (31%) from the final analyses. This certainly reduced the statistical power of the study to come to a meaningful conclusion.

Third, even though the ductal morphology and the stone size had been described, the location of intraductal calculi was not described in detail either in this article or in the original ESCAPE trial. It is known that the location of the intraductal calculi could impact technical and clinical success of extracorporeal shock wave lithotripsy (ESWL).<sup>3</sup> Moreover, the distribution of pancreatic duct strictures between the 2 study groups was also not reported. It is known that the presence of strictures predicts pain recurrence after ESWL.<sup>4</sup>

Fourth, neural sensitization is a well-recognized phenomenon in long-standing chronic pancreatitis (CP) that can modulate pain responses.<sup>5</sup> Absence of data on neural sensitization makes it difficult to interpret the data on long-term efficacy of both surgery and endotherapy. However, identification of pancreatic neuropathic pain at the bedside is still experimental, and no standardized recommended technique exists at this time.

Based on these premises, we feel it is not yet prime time to recommend early surgery as the therapeutic criterion stan-

dard, while ignoring the potential role of endotherapy, for painful CP with a dilated duct and intraductal stones.

**Rupjyoti Talukdar, MD**  
**Guduru Venkat Rao, MS**  
**Duvuur Nageshwar Reddy, MD, DM**

**Author Affiliations:** Department of Medical Gastroenterology, Asian Institute of Gastroenterology Hospitals, Telangana, India (Talukdar, Reddy); Department of Surgical Gastroenterology, Asian Institute of Gastroenterology Hospitals, Telangana, India (Rao).

**Corresponding Author:** Rupjyoti Talukdar, MD, Asian Institute of Gastroenterology Hospitals, Mindspace Road, Gachibowli, Hyderabad 500032, Telangana, India ([rup\\_talukdar@yahoo.com](mailto:rup_talukdar@yahoo.com)).

**Published Online:** April 2, 2025. doi:[10.1001/jamasurg.2025.0419](https://doi.org/10.1001/jamasurg.2025.0419)

**Conflict of Interest Disclosures:** None reported.

1. Issa Y, Kempeneers MA, Bruno MJ, et al; Dutch Pancreatitis Study Group. Effect of early surgery vs endoscopy-first approach on pain in patients with chronic pancreatitis: the ESCAPE randomized clinical trial. *JAMA*. 2020;323(3):237-247. doi:[10.1001/jama.2019.20967](https://doi.org/10.1001/jama.2019.20967)
2. van Veldhuisen CL, Kempeneers MA, de Rijk FEM, et al; Dutch Pancreatitis Study Group. Long-term outcomes of early surgery vs endoscopy first in chronic pancreatitis: follow-up analysis of the ESCAPE randomized clinical trial. *JAMA Surg*. Published online February 1, 2025. doi:[10.1001/jamasurg.2024.5182](https://doi.org/10.1001/jamasurg.2024.5182)
3. Tandan M, Talukdar R, Reddy DN. Management of pancreatic calculi: an update. *Gut Liver*. 2016;10(6):873-880. doi:[10.5009/gnl15555](https://doi.org/10.5009/gnl15555)
4. Gurav N, Jagtap N, Koppoju V, et al. Predictors of persistent pain after extracorporeal shockwave lithotripsy for painful chronic calcific pancreatitis. *Endoscopy*. 2024;56(6):406-411. doi:[10.1055/a-2252-9920](https://doi.org/10.1055/a-2252-9920)
5. Singh VK, Yadav D, Garg PK. Diagnosis and management of chronic pancreatitis: a review. *JAMA*. 2019;322(24):2422-2434. doi:[10.1001/jama.2019.19411](https://doi.org/10.1001/jama.2019.19411)

**In Reply** We appreciate the opportunity to respond to the letter from Talukdar and colleagues. They argue against recommending early surgery as the criterion standard in patients with chronic pancreatitis with a dilated pancreatic duct, highlighting 4 points.

First, Talukdar and colleagues would like the effect size to be reported, which may be more clinically relevant than the *P* value. The effect size was not reported, although this could provide clinically relevant information, as in this follow-up study we report the same primary outcome as the initial trial report with 1.5-year follow-up. Second, the authors highlight the exclusion of 27 patients, reducing statistical power. We acknowledge the concern regarding the loss to follow-up and its potential impact on the statistical power of the study, as reported in the Discussion section. This is a notable limitation that was already highlighted as such. However, the dropout rate was similar among the 2 groups (ie, by mortality and no informed consent), which helps mitigate any potential for systematic bias. While the reduction in sample size may limit

the strength and statistical power of some findings, the remaining data still offer valuable insights and show strong statistical difference between treatment strategies in several factors, such as a lower Izbicki pain score, a higher rate of patient-reported complete pain relief, and more patients reported to be very satisfied with their treatment in the early-surgery group. Third, the authors mention the lack of detailed morphological data (eg, stone location, stricture distribution), which could impact extracorporeal shock wave lithotripsy outcomes. Morphological factors in chronic pancreatitis are indeed important in assessing the efficacy of both surgical and endoscopic treatments, and for that reason we did provide the morphological information in the Supplement of the original ESCAPE trial (eTable 7).

Finally, they emphasize the role of neural sensitization in interpreting long-term outcomes in chronic pancreatitis, which is indeed important, as neural sensitization can significantly influence pain perception and overall treatment response in chronic pancreatitis. However, as noted by the authors, assessing neural sensitization remains challenging, as no standardized or universally accepted techniques are available. Future reliable assessment of neural sensitization would provide valuable insights into its impact on long-term treatment efficacy and patient quality of life.

In summary, based on the considerations outlined above, we found no convincing arguments that challenge our conclusion that surgery is superior to an endoscopy-first approach in patients with painful chronic pancreatitis with a dilated main pancreatic duct.

Given the recent advancements in endoscopic techniques and the recent primarily laparoscopic approach for surgery, the Dutch Pancreatitis Study Group is currently initiating the next ESCAPE trial, the ESCAPE-2 trial. In the ESCAPE-2 trial, up-to-date surgery will be compared with up-to-date

endoscopy techniques in patients with painful chronic pancreatitis with a dilated main pancreatic duct to clarify the exact role of each approach in managing these patients.

**Charlotte L. van Veldhuisen, MD**  
**Marja A. Boermeester, MA, MD, PhD**  
**Yama Issa, MD, PhD**

**Author Affiliations:** Amsterdam Gastroenterology Endocrinology Metabolism, Amsterdam UMC, location University of Amsterdam, Amsterdam, the Netherlands (van Veldhuisen, Boermeester); Department of Research and Development, St Antonius Hospital, Nieuwegein, the Netherlands (van Veldhuisen); Department of Surgery, Amsterdam UMC, location AMC, University of Amsterdam, Amsterdam, the Netherlands (Boermeester); Department of Surgery, Leiden University Medical Center, Leiden, the Netherlands (Issa).

**Corresponding Author:** Charlotte L. van Veldhuisen, MD, Department of Surgery, Amsterdam UMC, University of Amsterdam, De Boelelaan 1117 (ZH-7F), 1081 HV Amsterdam, the Netherlands (c.l.vanveldhuisen@amsterdamumc.nl).

**Published Online:** April 2, 2025. doi:10.1001/jamasurg.2025.0422

**Conflict of Interest Disclosures:** Dr Boermeester reported institutional funds for a nonrelated study and consultancy work for Johnson & Johnson; institutional grants for an investigator-initiated study from Solvatum and TelaBio; and consultancy work for AngioDynamics, Becton Dickinson, Mölnlycke Health Care, and Smith & Nephew. No other disclosures were reported.

**Additional Contributions:** Marinus A. Kempeneers, MD, PhD, and Marc G. Besselink, MD, PhD (both Amsterdam University Medical Center, University of Amsterdam), also contributed to this letter.

## CORRECTION

**Error in Equation:** In the Original Investigation titled "Validated Integration of Tumor Deposits in N Staging for Prognostication in Colon Cancer,"<sup>1</sup> published online first February 5, 2025, and in the April 2025 issue, the equation in the Methods section had a typographical error, where a plus sign should have been a minus sign. This article has been corrected online.

1. Sassun R, Sileo A, Ng JC, et al. Validated integration of tumor deposits in N staging for prognostication in colon cancer. *JAMA Surg*. Published online February 5, 2025. doi:10.1001/jamasurg.2024.6729