statistical underpinnings of an equivalency or noninferiority trial require that an initial difference in outcomes between groups be designated as a clinically relevant difference. Adhering to a strict interpretation of the results of the equivalency trial, one can only make conclusions with respect to the difference in outcomes initially designated. For our study, we chose 6% as that designated difference, to avoid a potentially meaningless difference in infection rate between groups, which might be statistically different but not clinically relevant. This was balanced with the sample size requirements for a smaller equivalence threshold. In Dr Lee’s example for comparing 9% infection rate for paint-only versus 4% in paint-plus-scrub, the sample size requirements would be approximately 650 patients per group (1,300 patients total).

We have contributed to the literature a controlled clinical trial that was designed to test the idea that preoperative scrubbing of skin with povidone-iodine soap adds no incremental protection against wound infection. We do not agree with Dr Lee that our results have the same interpretation as a hypothetical trial, where the actual infection frequency was 9% in the paint-only arm and 4% in the paint-plus-scrub arm. Although Dr Lee’s worst-case outcomes would be within the tolerance of our 6% equivalence threshold based on our current results and the results of previous trials, that specific outcome would be unlikely given the data that has been reported as of this writing. Admittedly, Dr Lee is correct that the interpretation of our results has not added to the possible knowledge-space: povidone-iodine scrubbing might add benefit, might have no effect at all, or might actually increase infection likelihood. Statistical reasoning does not deal in perfect knowledge states. It can lead to conclusions that speak to the likelihood of outcomes. We would argue that our data have shown that the advantage of povidone-iodine scrubbing over paint-only is minimal at best because it is the most likely interpretation.

Despite the results of even the most rigorously designed single clinical trial, the thoughtful clinician will always weigh the pros and cons of altering his or her clinical practice. Results of our single clinical trial must be interpreted in the context of the four earlier clinical trials available for review, all of which are cited in our publication. Each of these was a negative trial, and each trial compared the “gold standard” scrub-plus-paint to something different and often less than scrub-plus-paint. In view of this body of literature and our clearly negative clinical trial, an objective observer who is not lost in the vagaries of statistical minutiae, can conclude that a reasonable argument can be made for abandoning scrub-and-paint.

## Delayed Massive Hemorrhage after Pancreatectoduodenectomy: A New Therapeutic Approach

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We read with great interest the series of delayed massive hemorrhages after pancreatectoduodenectomy reported by Tien and colleagues1 in your journal. They have confirmed that delayed massive hemorrhage after pancreatectoduodenectomy, often associated with septic complications secondary to leakage or intraabdominal abscess, is still a frequent event carrying a high mortality rate. After the failure of conservative management, final management can be either radiologic or surgical, as stated by Tien and colleagues.1 Although radiologic management is partly dependent on resuscitation facilities at the department of radiology and the prompt availability of experienced interventional radiologists, surgical management is much more invasive and brings with it high morbidity and mortality, even if it succeeds in stopping the bleeding. But there is a pharmacologic agent that can be used as rescue treatment in case of massive bleeding: recombinant activated factor VII (rFVIIa), which we used to treat a case of delayed massive hemorrhage after pancreatectoduodenectomy.

Recombinant FVIIa is a major alternative for management of hemophilic patients with inhibitors.2 More recently, it has been used off-label to control bleeding in patients with trauma or other massive life-threatening hemorrhage, and to reduce blood loss in surgical patients with normal coagulation.3-5 Recombinant FVIIa binds to activated platelets independently of tissue factor. The resulting stimulation of an exaggerated early thrombin burst at sites of vascular injury makes it an attractive potential treatment for massive, uncontrolled bleeding.
An 82-year-old woman presented with a diagnosis of adenocarcinoma of the head of the pancreas underwent a pylorus-preserving pancreaticoduodenectomy. During the postoperative course, a benign pancreatic fistula developed that was treated conservatively. On the 23rd postoperative day, a delayed massive hemorrhage occurred without any previously evident “sentinel bleed.” Fresh blood appeared in the abdominal drainage located close to the pancreaticojejunostomy followed by emission of red blood with stools. A CT scan showed no active abdominal bleeding, aneurysm, or pseudoaneurysm of visceral arteries. Despite administration of 4 U of packed red cell concentrates and 4 U of fresh frozen plasma, the hemoglobin dropped, suggesting a persistent hemorrhage. NovoSeven (Novo Nordisk) was given intravenously at a dose of 40 µg/kg body weight. The hemoglobin continued to drop slowly during the next 6 hours, suggesting a persistent hemorrhage. NovoSeven was readministered intravenously at a dose of 90 µg/kg body weight. This additional application of rFVIIa stabilized the hemoglobin level; no more transfusion was needed, and the patient left the hospital 15 days later.

Although indications for NovoSeven in acute delayed massive bleedings have not yet been formally evaluated, this report suggests that rFVIIa could be used effectively in this setting, avoiding interventional radiology procedures or surgery. The concern that rFVIIa might cause thrombotic events is reasonable given that this agent is administered at a concentration 1,000-fold higher than normal, but clinical evidence published to date has shown that the incidence of adverse events is < 1%.4

This experience shows interesting findings, but additional research is needed before the safety and effectiveness of rFVIIa in all such patients can be confirmed.

The authors of the article have no experience with recombinant activated factor VII, so declined to reply.

REFERENCES

Does the TNM Staging System for Esophageal Cancer Need Revision?

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We commend Kunisaki and colleagues1 for their thought-provoking article on the development of an appropriate staging system for esophageal cancer in a recent issue of the Journal. There have been numerous articles2,3 in recent times on the issue that bring into focus the pitfalls in the existing TNM staging system. There is a lack of data correlating pathology with overall survival, which looks beyond the present TNM system, and this article attempts to evaluate the ability of other staging systems to do so. Though the article does not clearly demonstrate the superiority of one system over the other, it infuses new ideas into the debate and gives it some direction. It is common experience that patients with a lower third esophageal malignancy with metastasis to supracarinal lymph nodes fare worse than those with a lower paraesophageal nodal metastasis. Similarly, patients with fewer metastatic nodes do better than those with multiple metastatic nodes. Hence, logically, the location and the number of metastatic lymph nodes should have an impact on survival. These theories have also been backed up by some studies.4 There have also been studies5 emphasizing the importance of the ratio of metastatic to total lymph nodes dissected. Whether this ratio will have a widespread, universal impact is difficult to ascertain because of the wide variability of lymph node sampling and dissection by surgeons and, more importantly, pathologists.

The only drawback of this study is the paucity of numbers. We suggest a large multicentric international