lymphadenectomy. According to the literature, we think that different maps based on histology (squamous cell carcinoma or adenocarcinoma), neoadjuvant therapy (performed or not), and tumor site (upper thoracic, middle thoracic, lower esophagus, or esophagogastric junction) could be made.

Moreover, we would like to underline the importance of the map of nodal metastasis after neoadjuvant therapy. In fact, the rate of esophageal squamous cell carcinoma treated with neoadjuvant therapy has increased since the 1980s, and neoadjuvant therapy followed by esophagectomy currently is performed by most clinicians.⁵ A specific map for this therapy pattern is worthwhile because the distribution of nodal metastasis could be affected by preoperative treatment,⁴ and it requires a different map compared with patients who undergo only surgery.

This strategy could suggest the most frequently involved lymph nodes in each combination of the above-mentioned variables, leading to an improvement of the effectiveness of surgery. Therefore, further studies are needed to explore the reasonableness of this idea, to exchange opinions among research groups, and to gather information for map construction.

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References

1. Li B, Chen H, Xiang J, Zhang Y, Li C, Hu H, et al. Pattern of lymphatic spread in thoracic esophageal squamous cell carcinoma: a single-institution experience. *J Thorac Cardiovasc Surg.* 2012;144:778-86.
2. Peyre CG, Hagen JA, DeMeester SR, Altorki NK, Ancona E, Griffin SM, et al. The number of lymph nodes removed predicts survival in esophageal cancer: an international study on the impact of extent of surgical resection. *Ann Surg.* 2008;248:549-56.
3. Liu YP, Ma L, Wang SJ, Chen YN, Wu GX, Han M, et al. Prognostic value of lymph node metastases and lymph node ratio in esophageal squamous cell carcinoma. *Eur J Surg Oncol.* 2010;36:155-9.
4. Castoro C, Scarpa M, Cagol M, Ruol A, Cavallin F, Alfieri R, et al. Nodal metastasis from locally advanced esophageal cancer: how neoadjuvant therapy modifies their frequency and distribution. *Ann Surg Oncol.* 2011;18:3743-54.
5. Ruol A, Castoro C, Portale G, Cavallin F, Sileni VC, Cagol M, et al. Trends in management and prognosis for esophageal cancer surgery: twenty-five years of experience at a single institution. *Arch Surg.* 2009;144:247-54.

<http://dx.doi.org/10.1016/j.jtcvs.2012.11.089>

Reply to the Editor:

We thank Cavallin and colleagues for their interest in our article.

Although controversies still remain in the management of esophageal cancer, and neoadjuvant therapy has not been widely conducted in China, it is obvious that neoadjuvant therapy plays an important role. Over the past decade, treatment strategy has changed a lot in our center. Between 2000 and 2004, the McKeown procedure with a 3-field lymphadenectomy was performed unselectively to all patients with esophageal cancer. Since 2005, Ivor-Lewis esophagectomy with 2-field lymphadenectomy has been widely performed, and the 3-field lymphadenectomy procedure was selectively applied on the basis of ultrasound and computed tomography information considering a higher risk of complications. Although adjuvant chemoradiotherapy after surgery was routinely performed for advanced cancers, the prognosis remains disappointing in our experience. Therefore, we also think neoadjuvant therapy could improve the prognosis of surgery.

As mentioned in our article, only 30 of 1491 patients with squamous cell carcinoma (SCC) received chemotherapy or radiotherapy before surgery between 2006 and 2010 in our center.¹ There are several factors. Surgeon's preference may be the first issue. The idea of neoadjuvant

therapy for esophageal cancer has not been widely accepted by surgeons in China. Different pathologic patterns from the West and increased risk of complications may be 2 important factors influencing their treatment decision making. Because most patients with esophageal cancer came from poor rural areas, heavy treatment costs and inadequate medical insurance would be the second reason. However, in 2011, China spent only 4.98% of its gross domestic product on health care. On the other hand, patients traditionally prefer to receive resection when the cancer is pathologically confirmed, so patients' compliance for neoadjuvant therapy would be another major factor. Finally, lack of prospective trials was the most important problem. One latest study showed that preoperative chemoradiotherapy could improve survival among patients with potentially curable esophageal cancer.² However, the results were limited because of the small sample of patients with SCC. More randomized trials with a larger sample for neoadjuvant therapy for those with SCC are still needed.

At present, the treatment strategy for esophageal cancer is not uniform in China, not only the administration of neoadjuvant therapy but also the choice of surgical approach, reconstruction route, and extent of lymphadenectomy. Considering the frustrating prognosis, efforts are necessary to improve the survival. Randomized clinical trials are being performed in our center. Because the left thoracic procedure is widely performed in China,³ one study comparing the left and right thoracic approaches (ClinicalTrials.gov identifier, [NCT01047111](https://clinicaltrials.gov/ct2/show/study?term=NCT01047111)) has enrolled 300 patients with middle and lower esophageal cancer since 2010, and follow-up information is being collected. Another study comparing 3-field lymphadenectomy and 2-field lymphadenectomy is ready to begin and has been approved by the

institutional review board of Fudan University Shanghai Cancer Center. Prospective randomized research of neoadjuvant therapy will be performed soon. We are willing to share the results with our colleagues throughout the world and relate our experience for the treatment of esophageal cancer.

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References

1. Li B, Chen H, Xiang J, Zhang Y, Li C, Hu H, et al. Pattern of lymphatic spread in thoracic esophageal squamous cell carcinoma: a single-institution experience. *J Thorac Cardiovasc Surg.* 2012;144:778-86.
2. van Hagen P, Hulshof MC, van Lanschot JJ, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BP, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med.* 2012;366:2074-84.
3. Li B, Guo Q, Yang H, Guan J, Liu Z, Li S, et al. Left thoracoabdominal approach in surgical treatment of adenocarcinoma of the esophagogastric junction in the Northern Henan Province of China. *Dig Surg.* 2011;28:2-8.

<http://dx.doi.org/10.1016/j.jtcvs.2012.12.050>

METHYLENE BLUE, SEROTONERGIC SYNDROME, AND HEART TRANSPLANT To the Editor:

Grubb and colleagues¹ report a case of a 60-year-old man with history of nonischemic cardiomyopathy and end-stage heart failure who underwent placement of a left ventricular assist device (LVAD) and replacement of a mechanical aortic valve with a porcine prosthesis complicated by multiple driveline infections. The heart transplant was the last option. During the operation, the authors reported “episodes of hypotension during the extensive lysis of adhesions for

[LVAD] removal. Intermittent boluses of phenylephrine were administered to maintain a sufficient mean arterial pressure.” Subsequently, a methylene blue (MB) 1 mg/kg bolus followed by continuous infusion of 0.5 mg/kg/hour was administered. Postoperatively, the patient presented signals of serotonin syndrome, presumably a consequence of an interaction between MB and antidepressant medications.

This report has two crucial points: the possibility of serotonin syndrome triggered by the association MB and antidepressants, and the routine use of MB to handle vasoplegia in the milieu of heart transplant. Kofidis and colleagues² reported the first experience of vasoplegia treatment with MB after heart transplant and pointed out that this drug deserves attention because of its catecholamine-saving effect, thus preventing possible malperfusion. Kofidis and colleagues’ report is unique in the literature regarding using MB to treat vasoplegia associated with heart transplant.

In 2009, my colleagues and I published an article³ discussing 15 years of questions, answers, doubts, and certainties regarding MB for vasoplegic syndrome treatment in heart surgery. In summary, our report shared that heparin and angiotensin-converting enzyme inhibitors are risk factors; in the recommended doses it is safe (the lethal dose is 40 mg/kg); the use of MB does not induce endothelial dysfunction; the MB effect appears in cases of nitric oxide up-regulation; MB is not a vasoconstrictor—by blocking the cyclic guanosine 3, 5-monophosphate (cGMP) pathway it releases the cyclic adenosine monophosphate (cAMP) pathway, facilitating the norepinephrine vasoconstrictor effect; the most used dosage is 2 mg/kg administered intravenously as a bolus followed by the same continuous infusion because plasmatic concentrations strongly decays in the first 40 minutes; and there is a possible window of opportunity for MB’s effectiveness.³

To circumvent the morbidity and mortality associated with vasoplegic syndrome Grubb and colleagues¹ implemented an intraoperative protocol that includes administration of MB for vasoplegic syndrome resistant to vasopressor drugs. Because serotonin syndrome only occurs in a small percentage of patients and is treatable with benzodiazepines and supportive care, and the possibility of serotonin syndrome is less than the risk of untreated vasoplegia and potential end-organ injury and graft loss, we have continued to include MB in the management of severe vasoplegic syndrome.

I congratulate Grubb and colleagues for reporting the association between MB and antidepressants that may cause serotonin syndrome. Although, to be honest, as a proponent of the use of MB^{4,5} the purpose of my letter is to suggest Grubb and colleagues publish their MB experience in heart transplant. It would be a valuable contribution to the cardiac surgery literature.

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References

1. Grubb KJ, Kennedy JL, Bergin JD, Groves DS, Kern JA. The role of methylene blue in serotonin syndrome following cardiac transplantation: a case report and review of the literature. *J Thorac Cardiovasc Surg.* 2012;144:e113-6.
2. Kofidis T, Strüber M, Wilhelmi M, Anssar M, Simon A, Harringer W, et al. Reversal of severe vasoplegia with single-dose methylene blue after heart transplantation. *J Thorac Cardiovasc Surg.* 2001;122:823-4.
3. Evora PR, Ribeiro PJ, Vicente WV, Reis CL, Rodrigues AJ, Menardi AC, et al. Methylene blue for vasoplegic syndrome treatment in heart surgery: fifteen years of questions, answers, doubts and certainties. *Rev Bras Cir Cardiovasc.* 2009;24:279-88.
4. Andrade J, Batista M, Evora PR, Tavares JR, Buffolo E, Ribeiro EE, et al. Methylene blue administration in the treatment of the vasoplegic syndrome after cardiac surgery. *Rev Bras Cir Cardiovasc.* 1996;11:207-14.
5. Evora PR, Ribeiro PJ, de Andrade JC. Methylene blue administration in SIRS after cardiac operations. *Ann Thorac Surg.* 1997;63:1212-3.

<http://dx.doi.org/10.1016/j.jtcvs.2012.11.090>