Surgical treatment of esophageal cancer - Reply (letter)

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an association in a population of 298 Italian women. The population they studied was much smaller than ours, and the background characteristics, including conventional risk factors, of the Italian women are not described.

Given that our controls were recruited from among persons who had visited participating hospitals, they had conventional risk factors, including hypertension, diabetes mellitus, hypercholesterolemia, and smoking, but they had no history of coronary artery disease. Susceptibility genes for myocardial infarction can be identified from differences in polymorphisms between persons with conventional risk factors but no history of myocardial infarction and those with both risk factors and a history of myocardial infarction. In addition, we examined the relation of the plasminogen-activator inhibitor type 1 polymorphism to myocardial infarction by multivariate logistic-regression analysis with adjustment for age, body-mass index, and the prevalence of smoking, hypertension, diabetes mellitus, hypercholesterolemia, and hyperuricemia. Furthermore, the distribution of plasminogen-activator inhibitor type 1 genotypes in our controls was in Hardy–Weinberg equilibrium. Our controls were thus adequate for the analysis performed. Although the association of the 4G–668/5G polymorphism of the plasminogen-activator inhibitor type 1 gene with myocardial infarction remains controversial, it cannot be ruled out by the results of Mannucci et al.

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Surgical Treatment of Esophageal Cancer

TO THE EDITOR: Hulscher and colleagues’ success with transhiatal and transthoracic surgical approaches for esophageal carcinoma (median survival, 1.8 and 2.0 years, respectively) explains why they found no difference between the two procedures (Nov. 21 issue).1 Both participating institutions were high-volume centers for esophagectomy procedures (more than 50 per year), with a lower perioperative mortality rate (<4 percent) than that in the Medical Research Council trial (10 percent).2,3 Thus, over a six-year period, at least 600 such operations must have been conducted. However, the authors state that 263 patients were eligible. It is difficult to imagine that the rest of the esophagectomy procedures (those that were not eligible) were performed for squamous-cell carcinoma of the esophagus or a benign condition (which would be rare in the West) or failed to meet the eligibility criteria.

In addition, the attrition rate of nearly 16 percent is not explained. There must have been some upward stage migration in the transthoracic–esophagectomy group, since 69 percent of the patients in that group had advanced disease, as compared with only 57 percent in the transthiatal group (P<0.01).

This may affect the analysis of overall survival. Although the trial did not set out to seek survival differences in patients with early esophageal carcinoma, readers may benefit from such information, especially when neoadjuvant treatment is being considered.2 The confounding effects on survival due to adjuvant chemotherapy (if received) are not highlighted.

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TO THE EDITOR: Hulscher et al. conclude that extended lymph-node dissection should be a standard component of esophagectomy. However, preoperative chemoradiotherapy may have a greater effect on outcome than extended lymphadenectomy and may obviate the need for extended lymphadenectomy. In many countries, the management of esophageal cancer includes chemotherapy and radiotherapy, and Hulscher and colleagues do not state what proportion of each group in their trial received postoperative adjuvant or salvage therapies that may have affected the calculation of costs or the survival curves.

Extended lymphadenectomy was associated with a 31 percent rate of local–regional failure, and the median survival rates were 1.8 and 2.0 years in the transhiatal- and transthoracic-esophagectomy groups, respectively. We and our colleagues at Johns Hopkins, in Baltimore, saw local–regional failure as a component of initial failure in only 8 of 90 patients (9 percent) treated with two consecutive protocols that included neoadjuvant radiotherapy with cisplatin, protracted venous infusion of fluorouracil, and administration of 44 Gy of external-beam radiation, followed by transhiatal esophagectomy and subsequent adjuvant chemotherapy.1,2 With this treatment approach, the median and disease-specific survival rates for all the enrolled patients were 2.9 years and 4.9 years, respectively, and the 5-year overall and disease-specific survival rates were 40 percent and 49 percent.

In their accompanying editorial, Kitajima and Kitagawa state that “systematic lymph-node dissection has a role in the curative treatment of esophageal cancer.”3 It appears that superior local control and survival are possible with neoadjuvant chemoradiotherapy, transhiatal esophagectomy, and postoperative chemotherapy.

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THE AUTHORS REPLY: Our conclusion cannot be interpreted as a general recommendation of transthoracic esophagectomy. Identification of subgroups that have relatively high long-term benefit helps translate the general outcome of the trial into individualized decision making. Because we expected site-specific treatment effects, randomization was stratified according to the tumor site. Although we recognize the limitations of subgroup analysis, the long-term benefit of transthoracic esophagectomy is more substantial in patients with esophageal tumors (five-year survival advantage, 17 percent; 95 percent confidence interval, −3 percent to 37 percent) than in patients with junctional or cardiac tumors (five-year survival advantage, 1 percent). Therefore, we now consider transthoracic esophagectomy standard treatment for otherwise fit patients with potentially curable esophageal cancer, whereas transhiatal esophagectomy is the preferred approach in patients with junctional or cardiac cancer.

So far, five of six randomized trials failed to show that neoadjuvant chemoradiotherapy was associated with a survival advantage. Outcomes in studies using historical controls are overestimated. Preoperative chemoradiotherapy is still considered experimental, with contradictory results reported from mostly underpowered trials.3 None of the patients in our study received either adjuvant or neoadjuvant therapy. Palliative external radiotherapy (in 29 patients) or chemotherapy (in 7) was used in some patients who had a symptomatic recurrence.

Of the 682 patients who underwent surgical tumor resection at the two institutions during the study period, 431 had adenocarcinoma, of whom 168 were excluded on the basis of predefined criteria, 34 refused to participate, and 9 were erroneously not asked to participate. Indeed, hospital volume is inversely related to early postoperative mortality.2 This partly explains the difference in mortality reported by us (<4 percent in-hospital mortality) and the Medical Research Council (10 percent within 30 days).

Lymphadenectomy leads to upward stage migration. However, this does not affect the base-line similarity of the randomized groups and thus does
not affect the analysis of overall survival. Subgroup analysis of early stages (0 to IIB) combined showed a 19 percent five-year survival advantage after trans-thoracic esophagectomy, but this comparison is biased because of stage migration.

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THE EDITORIALISTS AND A COLLEAGUE REPLY: We essentially agree with Knisely et al. that a multimodal approach is crucial to improve survival in patients with esophageal cancer. Concurrent chemoradiotherapy is a breakthrough for locally advanced and unresectable disease. However, the significance of neoadjuvant chemoradiotherapy in terms of local control and a survival benefit in patients with potentially resectable esophageal cancer is still controversial. Were it possible to perform curative resection, it would surely be hard to justify the risk of neoadjuvant chemotherapy, including an increase in operative morbidity and late adverse effects. Of several randomized trials1-3 that compared neoadjuvant chemoradiotherapy followed by surgery with surgery alone, only one study, in which survival in the surgery-only group was very poor, showed an overall survival benefit associated with neoadjuvant chemoradiotherapy.¹ The additional benefit of neoadjuvant chemoradiotherapy would necessarily depend to a certain degree on the quality of lymph-node dissection. From this point of view, the rationale for performing transhiatal esophagectomy is questionable.

Although we are not proposing that uniform extended lymph-node dissection be a standard component of esophagectomy, we do suggest that transhiatal esophagectomy is not always the best option as a surgical component. On the other hand, a complete response (according to pathological examination) after neoadjuvant chemoradiotherapy is a significant predictor of improved survival. Therefore, an individualized, multimodal therapeutic plan based on biologic information to predict the response to adjuvant therapy seems desirable.

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Mass Treatment of Filariasis in New Guinea

TO THE EDITOR: Bockarie et al. (Dec. 5 issue)¹ provide encouraging new evidence that mass treatment with antifilarial drugs can interrupt transmission of Wuchereria bancrofti. However, their conclusion that this strategy can eliminate filarial lymphedema may be overly optimistic. Bockarie et al. credit mass treatment with an impressive 69 percent cure rate among a subgroup of persons who entered the study with lymphedema. However, the overall prevalence of lymphedema decreased only from 5 percent to 4 percent, suggesting that the incidence of new-onset lymphedema, presumably also filarial in origin, was substantial. Furthermore, this reduction in prevalence just reached statistical significance, and the denominator changed (from 1273 to 998), making it difficult to interpret the results.

Decreases in the prevalence of lymphedema have been observed previously after mass treatment with antifilarial drugs,²,³ but these earlier studies focused primarily on interrupting filarial transmission. Few details are provided on how lymphedema and coexisting conditions were assessed. Others have noted no such reduction in the prevalence of lymphedema after mass treatment.⁴,⁵ In a recent clinical trial, diethylcarbamazine had no effect on chronic lymphedema.⁶

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