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 transthoracic esophagectomy, but this comparison is biased because of stage migration.

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1. Kelsen D. Preoperative chemoradiotherapy for esophageal cancer. J Clin Oncol 2001;19:283-5.
2. van Lanschot JJB, Hulscher JBF, Buskens CJ, Tilanus HW, ten Kate FJW, Obertop H. Hospital volume and hospital mortality for esophagectomy. Cancer 2001;91:1574-8.

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 chemoradiotherapy, including an increase in operative morbidity and late adverse effects. Of several randomized trials[1-3] 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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1. Walsh TN, Noonan N, Hollywood D, Kelly A, Keeling N, Hennessy TPJ. A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. N Engl J Med 1996;335:462-7. [Erratum, N Engl J Med 1999;341:384.]
2. Bosset J-F, Gignoux M, Triboulet J-P, et al. Chemoradiotherapy followed by surgery compared with surgery alone in squamous-cell cancer of the esophagus. N Engl J Med 1997;337:161-7.
3. Ubra SG, Orringer MB, Turrisi A, Iannettoni M, Forastiere A, Strawderman M. Randomized trial of preoperative chemoradiation versus surgery alone in patients with locoregional esophageal carcinoma. J Clin Oncol 2001;19:305-13.

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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1. Bockarie MJ, Tisch DJ, Kastens W, et al. Mass treatment to eliminate filariasis in Papua New Guinea. N Engl J Med 2002;347:1841-8.

2. Partono F, Purnomo, Oemijati S, Soewarta A. The long term effects of repeated diethylcarbamazine administration with special reference to microfilaraemia and elephantiasis. Acta Trop 1981;38:217-25.
3. Meyrowitsch DW, Simonsen PE, Makunde WH. Mass diethylcarbamazine chemotherapy for control of bancroftian filariasis through community participation: comparative efficacy of a low monthly dose and medicated salt. Trans R Soc Trop Med Hyg 1996;90:74-9.
4. Ciferri F, Siliga N, Long G, Kessel JF. A filariasis-control program in American Samoa. Am J Trop Med Hyg 1969;18:369-78.
5. Fan PC, Peng HW, Chen CC. Follow-up investigations on clinical manifestations after filariasis eradication by diethylcarbamazine medicated common salt on Kinmen (Quemoy) Islands, Republic of China. J Trop Med Hyg 1995;98:461-4.
6. Das LK, Subramanyam Reddy G, Pani SP. Some observations on the effect of Dalfon 500 (micronized purified flavinoid fraction of *Rutaceae aurantiae*) in bancroftian filarial lymphoedema. Filaria J (in press).

TO THE EDITOR: Although the results reported by Bockarie et al. represent a proof of principle for the potential success of an elimination strategy,[1] we cannot ignore the presence of adult worms, since most subjects tested (>75 percent) still had antigenemia, although there were no new infections. According to an evaluation of the effects in India of the current strategy for the elimination of filariasis involving the mass administration of diethylcarbamazine alone or with albendazole, there was a significant reduction in antigenemia among young children but not in older age groups.[2] A quarter of the adults continued to have antigenemia. Greater efforts must be made to operationalize innovative advocacy for better compliance with treatment[2] and to identify better antifilarial drugs. We need to prevent a resurgence of transmission by the remaining nonsusceptible adult worms that can reproduce microfilariae with the assistance of persistent contact between vectors and humans.

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1. Ottesen EA. Major progress toward eliminating lymphatic filariasis. N Engl J Med 2002;347:1885-6.
2. Rajendran R, Sunish IP, Mani TR, et al. Influence of mass administration of diethylcarbamazine, alone or with albendazole, on the prevalence of filarial antigenaemia. Ann Trop Med Parasitol 2002;96:595-602.

THE AUTHORS REPLY: Addiss correctly notes that the decrease in the overall prevalence of lymphedema in the study population over the five-year study period was small (from 5 percent to 4 percent) relative to the 69 percent rate of reversal of disease in a subgroup examined at both the beginning and the end of the study. As he comments, the sample size used to calculate the change in the overall prevalence of lymphedema decreased from 1273 to 998. Persons with and persons without lymphatic disease migrated into and out of study villages over the five-year period. The change in the denominator between the first and fifth years thus reflects this phenomenon and the inherent difficulty of maintaining follow-up in a rural setting. For this reason, we reported data for the subgroup of adults with preexisting lymphedema for whom follow-up data were available during subsequent years.

To address the issue of new-onset lymphedema raised by Addiss, we identified 695 adults without lymphedema who were examined in both 1993 and 1998. Two of them had new-onset lymphedema, resulting in a five-year cumulative incidence of 0.003. We cannot comment on data in the cited article by Das et al. suggesting that diethylcarbamazine has no effect on chronic lymphedema, since this work is in press and unavailable to us.

With regard to the comments by Rajendran et al., our observation that more than 75 percent of the subsample tested for filarial antigenemia remained positive after three rounds of treatment does not indicate that we ignored the importance to filariasis control programs of eliminating lymphatic-dwelling adult worms. We reported a 76 percent decrease in the mean antigen level, suggesting that mass drug administration was effective in reducing the burden of adult worms but that few persons were cured of infection as indicated by conversion from antigen-positive to antigen-negative status. We had anticipated that only a small proportion of persons would become antigen-negative, because the worm burdens were expected to be high in this area, where filariasis is endemic, and because of existing estimates of diethylcarbamazine activity against adult *W. bancrofti* worms.[1-3] Cure of infection would presumably require additional years of mass treatment with currently available antifilarial drugs or the development of new drugs with greater activity against adult worms.

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1. Tisch DJ, Hazlett FE, Kastens W, Alpers MP, Bockarie MJ, Kazura JW. Ecologic and biologic determinants of filarial antigenemia in bancroftian filariasis in Papua New Guinea. J Infect Dis 2001;184:898-904.

2. Noroes J, Dreyer G, Santos A, Mendes VG, Medeiros Z, Addiss D. Assessment of the efficacy of diethylcarbamazine on adult Wuchereria bancrofti in vivo. Trans R Soc Trop Med Hyg 1997;91:78-81.
3. Dreyer G, Addiss D, Santos A, Figueredo-Silva J, Noroes J. Direct assessment in vivo of the efficacy of combined single-dose ivermectin and diethylcarbamazine against adult Wuchereria bancrofti. Trans R Soc Trop Med Hyg 1998;92:219-22.

High-Frequency Ventilation

TO THE EDITOR: In the studies of high-frequency ventilation reported in the August 29 issue by Johnson et al.[1] and Courtney et al.,[2] there were important differences in the application of conventional ventilation in the control groups, which may explain why these trials had conflicting results. The trial by Johnson et al. required conventional ventilation to be started at a rate of 60 breaths per minute, in accordance with previous studies of optimal mechanical ventilation.[3,4] Courtney et al., however, set 60 breaths per minute as the maximal rate, which made it likely that lower rates and therefore higher tidal volumes were used in most of their patients. This was aggravated by the universal use of flow sensors, because the additional 1 ml of dead space must be compensated for by higher tidal volumes in order to maintain the desired partial pressure of carbon dioxide. Thus, higher-than-necessary tidal volumes put the control group at a disadvantage. Strictly speaking, the trial by Courtney et al. shows only that high-frequency ventilation is superior to synchronized ventilation with a flow sensor and rates of less than 60 breaths per minute.

We have demonstrated that conventional ventilation, with the ventilatory pattern optimized to achieve minimal peak inspiratory pressure by starting with at least 60 breaths per minute, can match high-frequency ventilation in terms of the outcome (a 69 percent rate of survival without chronic lung disease with each approach).[5] These results are confirmed by Johnson et al.[1]

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1. Johnson AH, Peacock JL, Greenough A, et al. High-frequency oscillatory ventilation for the prevention of chronic lung disease of prematurity. N Engl J Med 2002;347:633-42.
2. Courtney SE, Durand DJ, Asselin JM, Hudak ML, Aschner JL, Shoemaker CT. High-frequency oscillatory ventilation versus conventional mechanical ventilation for very-low-birth-weight infants. N Engl J Med 2002;347:643-52.
3. Oxford Region Controlled Trial of Artificial Ventilation OCTAVE Study Group. Multicentre randomised controlled trial of high against low frequency positive pressure ventilation. Arch Dis Child 1991;66:770-5.
4. Pohlandt F, Saule H, Schröder H, et al. Decreased incidence of extra-alveolar air leakage or death prior to air leakage in high versus low rate positive pressure ventilation: results of a randomised seven-centre trial in preterm infants. Eur J Pediatr 1992;151:904-9.
5. Thome U, Kössel H, Lipowsky G, et al. Randomized comparison of high-frequency ventilation with high-rate intermittent positive pressure ventilation in preterm infants with respiratory failure. J Pediatr 1999;135:39-46.

TO THE EDITOR: Courtney et al. report that infants assigned to high-frequency oscillatory ventilation were successfully extubated earlier than infants assigned to conventional ventilation. The proportion of infants who were alive without chronic lung disease was 56 percent in the group treated with high-frequency oscillatory ventilation, as compared with 47 percent in the group treated with synchronized intermittent mandatory ventilation. The authors state that the study protocol required extubation in the group treated with synchronized intermittent mandatory ventilation "when infants' condition had been stable for 6 to 12 hours while they were receiving minimal ventilatory support . . . the FiO_2 [fraction of inspired oxygen] was no more than 0.25 and mean airway pressure no more than 5 cm of water." The criterion for the mean airway pressure appears to be too conservative in comparison with current practices in tertiary neonatal intensive care units, where infants are generally extubated at a higher mean airway pressure than in this study. The finding that the infants treated with high-frequency oscillatory ventilation were successfully extubated earlier than those treated with synchronized intermittent mandatory ventilation — a significant difference — might be attributable to this.

Furthermore, there was a small but significant drop in the incidence of chronic lung disease in the group treated with high-frequency oscillatory ventilation. It will be interesting to see whether the investigators follow these infants further and report the neurodevelopmental outcome at one or two years of age. Such data would show whether a drop in the incidence of chronic lung disease reflects an improved long-term neurodevelopmental outcome in infants treated with high-frequency oscillatory ventilation. To answer the question of whether high-frequency oscillatory ventilation is truly a better