GENERAL THORACIC SURGERY

EDITORIAL ON COMBINED THERAPY FOR SQUAMOUS CELL CARCINOMA OF THE ESOPHAGUS

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The next two articles in this issue of the Journal are two important studies on combined therapy for squamous cell carcinoma of the esophagus. In the Japan Clinical Oncology Group study,¹ postoperative chemotherapy with cisplatin and vindesine are compared with surgery alone for patients having undergone a transthoracic esophagectomy with extensive lymphadenectomy for cancer of the thoracic esophagus. Surgical survivors were randomized to receive postoperative chemotherapy or no further therapy. The sample size was sufficient to show a clinical difference if such occurred. No difference in long-term survival was detected between those treated by surgery alone and those treated by similar operations plus postoperative chemotherapy. Survival was slightly better in those with diseased lymph nodes treated by chemotherapy compared with the no treatment group, but the difference was not significant.

In the Hong Kong prospective randomized trial,² preoperative chemotherapy with cisplatin and 5-fluorouracil followed by resection was compared with the results of surgery alone for squamous cell carcinoma of the esophagus. This study was not limited to patients with potentially curable disease, and 11% in the chemotherapy and 5% in the control group did not undergo surgical treatment. Again, the long-term survival data showed no significant difference between the group randomized to receive chemotherapy versus the surgery-alone group. As in several other recent publications,^{3,4} those patients

responding to chemotherapy had a better prognosis after surgery than did the nonresponders who underwent resection. This difference was highly significant. Those responding to chemotherapy had a median survival significantly longer than did the entire surgery-alone group. Patients receiving chemotherapy (58% of the 60 undergoing resection, or 47% of those randomized to receive chemotherapy) had a partial or complete response and underwent clinical downstaging before the operation. However, for those patients undergoing curative resection (R_0 with or without preoperative therapy), no significant difference in survival could be detected, although the trend was favorable for the preoperative chemotherapy group. Clinical staging in the Hong Kong group did not include computed tomographic scans or endoscopic ultrasonography. These techniques are generally thought to improve the preoperative staging and define comparable patient groups more precisely.

What lessons can be learned from these two important randomized trials? Inasmuch as no prospective randomized trial of preoperative or postoperative adjuvant therapy for squamous cell carcinoma proves that overall results are better than with surgery alone, surgery alone remains the preferred treatment of choice. A number of articles have now been published which demonstrate that more extensive primary surgery for potentially curable disease yields better results than the limited types of resections performed routinely in the past and still in wide use.⁵⁻⁷

The role of adjuvant chemotherapy has value only in those patients who respond to such treatment. Unfortunately, these patients cannot be identified with any certainty before the trial of chemotherapy. Because there is no tumor on which to judge response in protocols offering postoperative treatment, there is no basis for recommending postoperative chemotherapy prophylactically after curative esophagectomy. A better argument can be made for not giving postoperative adjuvant chemotherapy until an actual recurrence develops. At such time

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Requested for publication March 13, 1996; received April 28, 1997; accepted for publication April 30, 1997.

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J Thorac Cardiovasc Surg 1997;114:203-4

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0022-5223/97 \$5.00 + 0 12/1/82922

postoperative chemotherapy/radiation therapy for the recurrence can be recommended.

In the arguments concerning preoperative chemotherapy, the Hong Kong group found that earlier or more favorable stages of cancer were more likely to respond partially or completely to preoperative chemotherapy. This is also the group of patients who have the best chance for survival after curative surgery alone. Inasmuch as no significant difference was detected in the results between surgery alone versus chemotherapy plus surgery in the more favorable cases, it is hard to justify any routine use of preoperative chemotherapy.

In carefully controlled trials performed in investigative centers, the opportunity remains to study the relationship between complete and partial responders to a variety and increasing numbers of potential markers for tumor responsiveness. If a chemotherapy response could be predicted by a pretreatment marker, those patients who would respond would certainly be candidates for preoperative therapy. Therefore it is essential that such trials continue, but only in the setting of randomized trials in which study of multiple tumor markers can be carried out and correlated with chemotherapy response. Preoperative chemotherapy is not justifiable as standard practice at this time.

Comparison of these two trials points out other difficulties in comparing results from different groups or centers. The extent of surgery performed in these two trials is different. The dosages of cisplatin used were different. And the methods of staging used were different both technologically and in the system of staging. In recent years the outlook for patients with esophageal cancer undergoing treatment has improved somewhat because of advances in surgical technique, including a more thor-

ough removal of the primary tumor and its lymphatic drainage to the neck, mediastinum, and abdomen. For selected patients who respond to chemotherapy, the outlook is also improved. These observations instruct us in the standardization of surgical techniques and they encourage the continuation of research trials with new and better types of chemotherapy yet to be introduced, improved methods for pretreatment staging, and identification of markers to determine which patients have a favorable prognosis for combined therapy.

REFERENCES

1. Ando N, Iizuka T, Kakegawa T, Isono K, Watanabe H, Ide H, Tanaka O, et al. A randomized trial of surgery with and without chemotherapy for localized squamous carcinoma of the thoracic esophagus. *J Thorac Cardiovasc Surg* 1997;114:205-9.
2. Law S, Fox M, Chow S, Chu K, Wong J. Preoperative chemotherapy versus surgery alone for squamous cell carcinoma of the esophagus: a prospective randomized trial. *J Thorac Cardiovasc Surg* 1997;114:210-7.
3. Roth JA, Pass HU, Flanagan MM, et al. Randomized clinical trials of preoperative and postoperative adjuvant chemotherapy with cisplatin, vindesine, and bleomycin for carcinoma of the esophagus. *J Thorac Cardiovasc Surg* 1988;96:242-8.
4. Kelsen DP, Minsky B, Smith M, et al. Preoperative therapy for esophageal cancer: a randomized comparison of chemotherapy versus radiation therapy. *J Clin Oncol* 1990;8:1352-61.
5. Hagen JA, Peters JH, DeMeester TR. Superiority of extended en bloc esophagectomy for carcinoma of the lower esophagus and cardia. *J Thorac Cardiovasc Surg* 1993;106:850-8.
6. Lerut T, De Leyn P, Coosemans W, et al. Surgical strategies in esophageal carcinoma with emphasis on radical lymphadenectomy. *Ann Surg* 1992;21:583-90.
7. Altorki NK, Girardi L, Skinner DB. En bloc esophagectomy improves survival for stage III esophageal cancer. *J Thorac Cardiovasc Surg*. In press.