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## Discussion

DR. HIRAM C. POLK, JR. (Louisville, Kentucky): Dr. Jurkiewicz, Dr. Copeland, Ladies, and Gentlemen. I consider it a personal honor to open the discussion of the paper by Dr. Woodward. He has been one of the premier clinical surgeons in this Association for a long time. I am willing to accept this as a norm, partly out of my respect for the kind of work he and Dr. Vogel do and partly out of the futility we have had with our own work in this field.

Let me ask a couple of questions for the discussion, and it will help clarify this, because I think the data are very persuasive as presented.

First of all, have you used preoperative endoscopic ultrasound to try to stage these patients? It sure does seem like that is a very precise thing and can tell you some things about both the operative management and even stage them so you can judge some of these effects more precisely.

Do you make an effort in the radiotherapy protocol to protect either end of the potential anastomosis from irradiation? The suggestion is that it is not a high-risk phenomenon. I would wonder if you do that.

Fourthly, how long have you left in the interval between the completion of the chemoradiotherapy and operation? I did not quite get that, and I think for many of us who would like to emulate that work, that's important.

You had a very low leak rate, and it seemed not to be influenced by the radiochemotherapy. On the other hand, I wonder if you had some of the dysphagia we have seen after this. And whether that is a technical issue or the results of therapy, I do not know.

Finally, I would be especially interested if you had any change in the ploidy that you noticed on the secondary biopsies? In the tumors that persist, did ploidy or the degree of differentiation change from what it had been preoperatively?

I guess there are two other points you could clarify—the combination of adeno and epidermoid carcinoma in this, is that useful? Did you see one better than the other? And did patients with cancer of the esophagogastric junction do better than those in the body of the esophagus?

This is tremendous work. I think most of us feel it was a privilege to hear it. Thank you.

DR. JOHN S. BOLTON (New Orleans, Louisiana): Thank you, Dr. Jurkiewicz.

We currently have a chorus of support based on multiple

small phase II studies for neoadjuvant therapy for esophageal cancer, and we have just heard several more voices in that chorus in the form of the papers presented by Dr. Wolfe and Dr. Woodward.

However, I must interject one note of caution, that the phase III randomized control study has not been done, and I believe still it should be done, because there are many potential sources of bias in studies such as the ones presented.

I'd like to focus on one potential bias that can be created by using historical controls. This is the experience of the Oschner Clinic from 1981 through 1994 with resection of esophageal cancer, during which time neoadjuvant therapy was used in only a handful of bulky tumors, judged to be marginally resectable or unresectable at the time of initial evaluation.

There has been a significant trend toward earlier diagnosis. In the last 5 years almost half of our patients are less than or equal to stage IIA and more than a quarter in the last 5 years actually stage I.

And based on fairly well documented 5-year survivals of 80% to 90% for stage I esophageal cancer, 40% to 50% for stage IIA and only 10% to 15% for stage IIB and greater, we might conservatively anticipate a doubling of survival in the later group if we had done a phase II neoadjuvant study, entering all patients in the later period.

And even if the chemoradiotherapy accomplished nothing, it would appear that we had significant improved survival over our historical controls.

I'd like to ask several questions of Dr. Woodward and Dr. Vogel.

To comment on the preoperative staging, how confident are you that the preoperative stages of the two groups which were sequential, not concurrent, are comparable?

Second, were there any surveillance cancers included? By that I mean patients with adenocarcinoma and Barretts who are identified at a preclinical stage by virtue of endoscopic monitoring.

And, finally, if I read the abstract correctly, 11 preoperative therapy patients were not resected. Actually, in the presentation it sounded like there were 15. And don't the authors feel that these patients should be included when comparing survival of patients receiving preoperative therapy with those not receiving preoperative therapy? Otherwise, you are comparing only responders and stable disease to the untreated group, and you are eliminating those patients who may have had progressive disease and then were not resectable. And this could introduce a serious bias. And if those 15 patients are included, what would this do to the survival results of the neoadjuvant group as a whole?

And, finally, an observation that early diagnosis in Barrett's cancer is easily achievable if the endoscope is a primary screening test for reflux and other upper gastrointestinal symptoms, you have a red flag literally identifying the patients at risk for cancer long before clinical cancer develops. And this is a significant development that is really changing the natural history of adenocarcinoma of the esophagus and requires us to be careful in judging the results of neoadjuvant studies in uncontrolled

series, particularly if pretreatment staging is not carefully performed and reported.

Thank you very much.

DR. ALAN LIVINGSTONE (Miami, Florida): Thank you, Dr. Jurkiewicz, Dr. Copeland. I would like to echo what Dr. Polk said. It's always a privilege to listen to an experience such as Dr. Woodward has shared with us. We all learn from it.

It's interesting that we all seem to be in accord today with the approach to esophageal carcinoma, but that, of course, is not reflected in the world's literature. There was a major study just published by the Japanese in September in the *Annals of Surgery* that approached this from a different perspective. They did not use any neoadjuvant chemotherapy whatsoever. Instead of advocating less surgery, they advocated more surgery. If a little bit is good, more is better. They, of course, are progressing to the concept of three-field dissection—cervical, mediastinal and, indeed, celiac axis dissections.

What is interesting to me, whenever I look at Japanese literature, is that I always wonder if we are comparing apples and oranges. They got significant benefit from radical lymphadenectomy with up to even eight lymph nodes involved. Of course, Dr. Woodward's experience, and indeed, Dr. Skinner's experience, has not supported this, and I would just like to know what Dr. Woodward thinks about it.

In the Japanese experience just reported, lymph node metastases to the celiac axis or to the cervical area, what we would classify in North America as stage IV disease, was curable in up to 10% of the patients with surgery alone. I would like Dr. Woodward's comments on this, please, and ask him what he thinks about extended lymphadenectomies.

I also would like to know if endoscopic ultrasound was used in preoperative staging or, indeed, whether or not laparoscopy was used. I notice that there were 20 of 123 patients, i.e., 16%, who were deemed unresectable, and I wonder if these were unresectable because of local conditions that might have been picked up with endoscopic ultrasound or whether they had metastatic disease to the liver which might have been picked up with laparoscopy.

The rest of the comments have been addressed by previous discussants. I would like to thank the Association for the privilege of making my comments.

DR. LARRY C. CAREY (Tampa, Florida): Thank you, Dr. Jurkiewicz, Dr. Copeland. This is a very stimulating presentation that we have heard, sort of dangles the bait out there about how important is this combined form of treatment and for whom do we use it and how do we use it?

I had the pleasure not very long ago of being on a program with Dr. David Carter, professor of surgery at Edinburgh. And he said—and I think quite aptly—if you throw a brick out the window and goes up, it isn't statistically significant, but it is certainly an interesting observation. And I think maybe we're seeing a little bit of that in this presentation—the bricks going up.

There are a couple of questions I would like to ask the authors.

The preoperative chemoradiation neoadjuvant therapy began seriously in 1983. But if you look at the manuscript in 1984 and 1987, no patients got pretreatment. And if you look at 1994, they all got pretreatment. I think it would help us if we could understand a little better what the selection criteria were. How did that happen? Did the patients refuse treatment? Was there a different kind of tumor? What made those years different from the average year in the study?

Secondly, is it worth resecting the patients who don't respond? I think there are two areas of question about the role of surgical treatment in these individuals. Do you operate on those who respond completely and have no evidence of residual tumor? Conversely, do you operate on those who do not respond at all? I mean, is their prognosis so grim that the operation is not worthwhile?

And then, finally, as you look at the biology of esophageal cancer, Dr. Woodward, do you think that perhaps we are beginning to see evidence that squamous and adenocarcinoma are really the same disease? And are we making a fuss about an issue that really is not important?

Thank you very much for the opportunity to discuss the paper.

DR. JOHN L. SAWYERS (Nashville, Tennessee): Thank you, Dr. Jurkiewicz and Dr. Copeland. I wanted to make a comment and then ask some questions.

The comment is basically on our experience at Vanderbilt University during the past 6 years in a prospective trial using neoadjuvant therapy consisting of cisplatin, 5-FU and leucovorin with concomitant 30 cGy of mediastinal radiation.

There have been 24% complete responders to this therapy, and the survival has been prolonged up to 5 years over historic controls. But multivariate analysis using Cox proportional hazards regression identify only younger age of operation, and pathologic stage as the independent predictors of improved survival in our patients.

Gender, race, tumor location, tumor histology, pretreatment clinical stage, type of resection, and complete response to neoadjuvant therapy were not associated with statistically significant differences in long-term outcome.

I would like to ask Dr. Woodward, in your Group A patients, 35 underwent combined radiation and chemotherapy. Was survival improved in this group, as compared with other patients in Group A who received only radiation or only chemotherapy?

Do you think long-term survival, that is, 5 years or more, will be improved in your patients who had a complete response to preoperative treatment? I gather you do, but that did not quite work out with us.

Was death in your patients downstaged to your no-tumor-found NT group due to distant metastasized disease? That has been our experience, as local recurrence has been a very rare finding.

DR. STEPHEN B. VOGEL (Closing Discussion): Thank you Dr. Jurkiewicz and Dr. Copeland. Let me attempt to answer all of the many questions as briefly as possible. In advance, I wish to thank all of the discussants.

It appears in our study, as in others, that there is a trend toward increased survival in the chemoradiation group compared with radiation only. In this paper, however, the numbers were such that the results were not significant, although the trend did exist.

As mentioned in the manuscript, other studies showed a similar trend. The Michigan group has an actual 5-year survival of 60% in the complete pathological response group with a minimum follow-up of almost 58 months.

Most of the deaths in our series were due to distant disease, with the exception of two patients who demonstrated local recurrence in the stapled-off portion of the stomach along the lesser curve and midway between the pylorus and anastomosis. This was undoubtedly due to residual submucosal disease at the time of surgery. Several local recurrences at the anastomotic site were in patients with proximal carcinoma.

In answer to Dr. Livingstone's questions and with only one exception, we had no 5-year cures in lymph node positive patients, even when the dissection appeared adequate. This may be the result of the transhiatal technique in that the distal dissection can be performed adequately but there is essentially no lymphadenectomy performed in the mid thorax. We did not perform laparoscopy before any of these procedures and with a few exceptions, the technique of endoscopic ultrasound was not used in preoperative staging. Also, we have no information as to tumor ploidy.

In terms of a bias, one person saw most of the patients, and chemoradiation was offered essentially to all patients. There was no attempt to place any patient in any particular group, and if there was an inadvertent bias, the tumor size was larger in the chemoradiation group. As to who should have surgery offered, essentially all patients were offered chemoradiation plus surgery. We felt that if surgery was not potentially curative, it offered excellent palliation. In view of the time in years for patient input, we underwent many changes in CT technology. There was no attempt to stage patients preoperatively. Most of the patients were entered prior to the common use of endoscopic ultrasound and spiral CT technology. For the future, however, we still recommend surgery for those patients who have a gross response rate to preoperative endoscopy and biopsy. Half of these patients, as noted in the manuscript, had microscopic disease within the wall of the esophagus. This was similar to other groups mentioned in the paper. Even lymph node positive patients can benefit from palliation. At the present time, we cannot distinguish between the complete patho-

logical response group and those patients with microscopic foci in the wall of the esophagus.

There were a large number of patients in this study with a history of Barrett's esophagus and a long history of EG reflux. There were no patients in this study with specific Barrett's esophagus and dysplasia. There were only three patients considered to have the earliest stages of carcinoma or *in situ* carcinoma.

I agree that there is a statistical bias because patients who did not undergo resection were eliminated from the response rate statistics. Certainly, including these patients would diminish the response rates.

In most cases, surgery was performed 4 to 6 weeks after radiation and/or chemotherapy. All anastomoses in the esophago-gastrectomy group were performed using the GIA stapling device in a side-to-side manner. Most of the transhiatal esophago-gastrectomy anastomoses were also performed with this technique when an appropriate amount of cervical esophagus could be maintained. This standardization of technique and the fact that all the anastomoses were performed by one surgeon may have contributed to the very low leak rate.

Our data are significantly different from the recent Japanese reports noting an increased survival in patients with positive nodes who underwent radical lymphadenectomy. Certainly, this radical approach could not be performed with transhiatal esophagectomy. If this trend continues, we may re-evaluate our surgical procedures.

Patients who demonstrate no or very little response to chemoradiation have very poor overall survival. Although the palliation is adequate in terms of tolerating a diet, survival figures might suggest that surgery could be eliminated if the ability to eat could be restored via other alternative methods.

In summary, we believe that patients with either adenocarcinoma or squamous cell carcinoma should undergo neoadjuvant therapy. A similar number of patients in each group responded well. Although our study is nonrandomized and at a single institution, our results are comparable to the randomized studies reported from the Michigan group. They reported a 60% 5-year survival in the complete pathological response group and a similar survival to ours in the "microscopic foci only" group after chemoradiation and surgery. We feel that both of these groups should be offered surgery because we cannot distinguish between the two at least over a several month time period.

I wish to thank the society for the opportunity of presenting and discussing this paper. Thank you.