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Downstaging of Esophageal Cancer After Preoperative Radiation and Chemotherapy

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Objective

This retrospective, nonrandomized review evaluates 125 patients with esophageal carcinoma (adenocarcinoma and squamous cell) who underwent either surgery only or preoperative chemotherapy and/or radiation therapy followed by surgery. Major end points were survival and postchemoradiation downstaging.

Methods

Forty-four patients underwent radiation therapy of 4500 cGy over 5 weeks. Fluorouracil and cisplatin were administered on the first and fifth week of radiotherapy. Ninety-eight patients underwent "potentially curative" resections—transhiatal esophagectomy (70), Lewis esophagogastrectomy (25), and left esophagogastrectomy (3). All patients with preoperative adjuvant therapy underwent endoscopy and biopsy before surgery.

Results

There were no differences in overall mortality (5%) or surgical complications in either group. Fourteen of 44 patients (32%) downstaged to complete pathologic response, with 5-year survival of 57%. Fifteen of 44 patients (34%) downstaged to microscopic residual tumor, with 1- and 3-year survival of 77% and 31%, respectively. Twenty-eight of 29 patients in the two downstaged groups were lymph node negative. Overall, 5-year survival in the adjuvant therapy plus surgery group *versus* surgery only was 36% and 11% ($p = 0.04$). Five-year survival in lymph node-negative adjuvant therapy and surgery patients was 49% ($p = 0.005$). Positive nodes in the surgery only group was 48% *versus* 23% in the adjuvant therapy and surgery group ($p = 0.02$).

Conclusion

Although retrospective and nonrandomized, these results suggest that preoperative chemoradiation results in significant clinical and pathologic downstaging, increases survival, and may sterilize local and regional lymph nodes, accounting for both downstaging and survival statistics.

Historically, esophageal cancer has had a poor prognosis, with overall 5-year survival rates of 10% to 15% and a wide range of surgical procedures, complications, and mortality.[1-3] Subcategories of patients, especially those with negative lymph nodes and small lesions, have increased survival but represent a small percent of all patients with esophageal cancer. Although surgical resection has always been the standard treatment for esophageal cancer, the use of concurrent, combined chemoradiation preoperatively in the early 1980s resulted in significant downstaging to a pathologic complete response in up to 24% of patients.[4-6] There were few long-term survivors, however, and most series were composed of patients with squamous-cell carcinoma. Recent trials, however, have demonstrated similar responses in downstaging patients with both epidermoid and adenocarcinoma with 5-year survival rates up to 34%.[7-11] In a recent series with a 58 month minimum follow-up, an actual 60% 5-year survival rate was reported in patients downstaging to pathologic complete response.[11] The effectiveness of concurrent combined chemoradiation in downstaging patients and increasing survival has led several groups to question the need for surgical resection.[12-14]

Early pathologic findings at this institution, in patients who underwent combined chemoradiation followed by surgery, led us to broaden our concept of significant clinical and pathologic response. We identified a group of respondents who had no identifiable tumor at preoperative endoscopy (and biopsy) but who were found to have one or several small microscopic foci of tumor within the wall of the resected esophageal specimen. Increased survival in this subgroup of patients (residual tumor) has been documented previously.[11] If this trend continues in other studies, questions concerning the need for surgical resection after chemoradiation will be more readily answered.

In this retrospective, nonprotocol, nonrandomized, single institution review, we attempted to evaluate the effectiveness of preoperative chemoradiation *versus* surgery alone in terms of tumor downstaging, survival, and lymph node status.

PATIENTS AND METHODS

Patients

From late 1979 through the first 6 months of 1994, 125 patients with "potentially resectable" esophageal carcinoma were evaluated. The tumor type and location are listed in Tables 1 and 2 and are grouped retrospectively into group A, those patients who underwent surgery after some combination of radiation therapy and/or chemotherapy and group B patients, who underwent surgery only. Radiation and/or chemotherapy will be termed adjuvant preoperative therapy. Adenocarcinoma was present in 58% and 57% of group A and B patients and represents 92% and 79% of the distal lesions in groups A and B, respectively. Figure 1 demonstrates the accrual of surgical patients in groups A and B. Preoperative adjuvant therapy began in 1983, with the number of patients slowly increasing until the 1990s. The intent was to offer combined radiation and chemotherapy to all appropriate patients who accepted the increased time before surgery. Fifty-nine patients underwent preoperative adjuvant therapy—combined radiation and chemotherapy in 37, radiation therapy in 17, and chemotherapy only in 5. Sixty-six patients underwent exploration without preoperative chemoradiation. Four patients in group

Table 1. ESOPHAGEAL CANCER GROUPS

	Total Patients	Group A: Chemotherapy/ Radiation/Surgery	Group B: Surgery Only
Proximal	13	7	6
Mid	27	15	12
Distal	85	37 Adenocarcinoma 34 (92%)	48 Adenocarcinoma 38 (79%)
Total	125	59	66

Table 2. TUMOR TYPE

	Chemotherapy/ Radiation/Surgery	Surgery Only
Squamous cell	20 (34%)	22 (33%)
Adenocancer	34 (58%)	38 (57%)
Undifferentiated cancer	3	1
Leiomyosarcoma	—	1
Squamous *in situ*	1	1
Adeno cancer *in situ*	—	1
Signet ring cancer	1	2
Total	59	66

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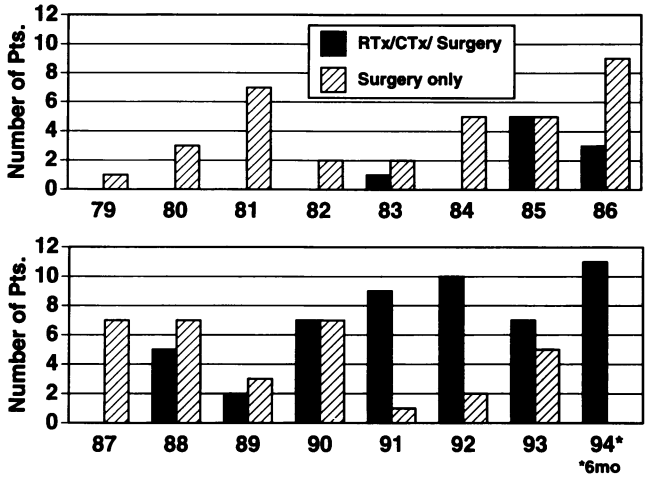

Figure 1. Patient accrual from 1979 through the first 6 months of 1994 and the number of patients undergoing preoperative radiation and/or chemotherapy.

A and 3 in group B had near total obstruction. These patients were admitted and underwent intravenous hyperalimentation, and four patients began chemoradiation during the hospitalization. In group A, there were 47 men and 12 women, with a mean age of 67 years (range 48–83 years). In group B, there were 50 men and 16 women, with a mean age of 64 years (range 51–81 years). The preoperative tumor size in groups A and B are shown in Figure 2.

All patients underwent preoperative barium upper gastrointestinal and computed tomography (CT) examinations. Group A patients underwent repeat endoscopy and biopsy after radiation or chemotherapy. In most cases, the CT examination was repeated preoperatively. Because of the change in technology between 1979 and the present, comparison of CT results are difficult. Increased resolution in the current spiral CT detects lymph nodes not seen or evaluated in the early 1980s. In general, mediastinal or celiac lymph nodes that were considered potentially resectable with the specimen did not alter the intent for adjuvant therapy or deter or influence surgical planning. These patients were not randomized on the basis of CT findings. Beginning mid to late 1980, the intent was to treat most, if not all, patients with adjuvant preoperative therapy, if they agreed.

Chemoradiation

Forty-three of 59 patients (73%) underwent radiation therapy at this institution. Twenty-seven percent received therapy in their local community after consultation and standardization of technique by our radiation oncology service. Patients were irradiated with parallel opposed fields using an anterior and posterior portal arrangement. The tumor was treated with 5 cm proximal and distal margins, 2- to 3-cm lateral margins. Patients were irradiated once daily to 4500 cGy in 25 fractions over 5 weeks. Chemotherapy in all cases consisted of cisplatin and fluorouracil administered during the first and fifth weeks of radiotherapy. The fluorouracil was given as a continuous 4-four day infusion and the cisplatin in a bolus dose on day 1 of chemotherapy. The patients treated in their home community received consultation from our medical oncology service. In most cases, patients were hospitalized for both chemotherapy regimens, but in recent years, a small number of patients were treated as outpatients.

Surgical Procedures

One hundred twenty-five patients considered potentially resectable underwent exploratory laparotomies. A total of 27 patients (group A, 15; group B, 12) were considered either unresectable or incurable because of numerous factors, including hepatic metastases, cirrhosis, extensive and diffuse positive lymphadenopathy, peritoneal carcinomatosis, or unresectable extension of esophageal tumor to contiguous structures. Six patients underwent either palliative resection or substernal gastric bypass. The remaining 98 patients underwent resection for "potential cure" with the following procedures: transhiatal esophagectomy (THE [70]), Lewis esophagogastrectomy (EG [25]), and left esophagogastrectomy (3). This represents a 78% resectability rate.

Lewis esophagogastrectomy was performed in the standard manner. In most cases, two separate incisions were used. After mobilization of the stomach, appropriate celiac nodes and paraesophageal tissue was mobilized with the specimen. The esophageal hiatus was

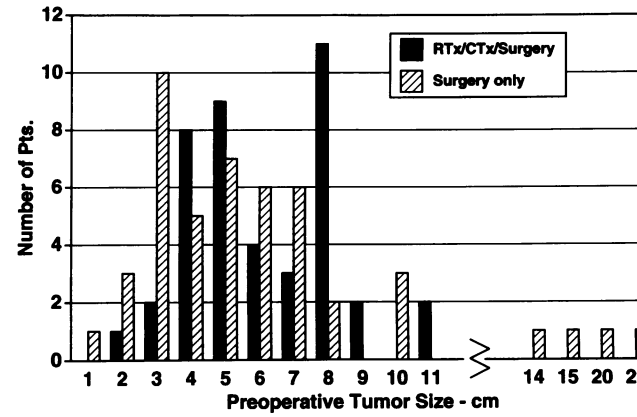

Figure 2. Tumor size in centimeters in all patients undergoing either preoperative adjuvant therapy or surgery without pretreatment.

widened. After right thoracotomy, the esophagus was mobilized to a level above the azygos vein. The entire stomach, still attached to the esophagus, was brought into the right chest, and the cardia and lesser curve were transected using the TA90 stapling device. Celiac nodes were kept on the cardia and esophageal side of the specimen. The gastric fundus was brought into the posterior mediastinum and the upper esophagus was placed side by side with the fundus. Then a side-to-side GIA (GIA, U.S. Surgical Corp., Norwalk, CT) anastomosis was performed, and the two openings were closed with a TA55 stapling device. The remaining fundus was then rolled around the anastomosis loosely in a Nissen type fashion. In three cases, left esophagogastrectomy for small EG junction lesions was performed through a single left thoracotomy incision. A similar side-to-side GIA anastomosis was performed. The abdominal portion of all transhiatal esophagectomy procedures was performed in a similar manner as the right EG procedure. At least two thirds of the mediastinal dissection was performed via the abdominal approach. In five cases, THE was abandoned because of the inability to safely dissect adherent paraesophageal tissue in the mid thorax. These patients were converted to a high right esophagogastrectomy. The remaining 70 patients underwent successful transhiatal esophagectomies. After mobilization of the stomach and celiac nodes, a cervical incision was made, and the proximal esophagus was mobilized. Mobilization was carried down circumferentially as the esophagus was pulled upward. Further dissection was performed transabdominally until the entire esophagus was free. In most cases, the distal esophagus was transected before placing the stomach through the posterior mediastinum. A TA90 stapling device was placed diagonally from the cardia down the lesser curve of the stomach and included the celiac vessels and lymph nodes with the esophageal side of the specimen. After transection, a long Penrose drain was placed from the cervical area down into the abdominal cavity and attached to the fundus of the stomach. The stomach was then brought through the posterior mediastinum into the cervical incision after removal of the entire esophageal specimen and cardia of the stomach out of the cervical area. In most cases, especially with mid to distal tumors, the fundus and esophagus were placed side to side and a "functional, end-to-end" anastomosis was performed using the GIA stapling device. In cases of high mid thoracic or cervical tumors, the fundus was anastomosed to the high cervical esophagus using a one layer end-to-side anastomosis. One of us (SBV) performed all the intrathoracic procedures, transhiatal dissections, and cervical anastomoses. This achieved a high level of surgical standardization.

Preoperative Endoscopy and Postoperative Pathology

All patients who underwent adjuvant preoperative therapy had repeat endoscopy and biopsy before surgery. A major or positive clinical response occurred when there was no gross evidence of tumor and biopsies yielded only a diagnosis of fibrosis. In many cases, the endoscopist documented ulceration or fibrosis at the site of the previous tumor. After surgery and removal of the specimen, three types of pathologic response were characterized: group 1) pathologic complete response when no tumor was found in the resected specimen; group 2) no evidence of gross tumor other than ulceration and fibrosis, but one or several microscopic foci within the wall of the esophagus; and group 3) residual gross tumor, although in many cases, it had diminished from preoperative size.

STATISTICS

Survival was calculated from the date of surgery. Lymph node status is reported in each subgroup. Major end points are survival and downstaging. Cumulative survival was determined using the Kaplan-Meier method[15] and p values were calculated by the method of Peto et al.[16]

RESULTS

Surgery

Of the 125 patients undergoing exploratory surgery, there were six deaths, for an overall mortality of 5%. Five deaths occurred in the 98 patients (5%) undergoing resection. The causes of death were as follows: acute myocardial infarction (1), acute pulmonary embolism (1), tumor erosion into bronchus and pulmonary sepsis (1), adult respiratory distress syndrome and pulmonary sepsis (2). There were no postoperative hemorrhages or emergency thoracotomies after transhiatal esophagectomy. There were seven cases of major adult respiratory distress syndrome, leading to prolonged therapy in the intensive care unit. There was no significant difference between group A (3) and group B (4) patients. There were no anastomotic leaks after esophagogastrectomy. There were 5/70 (7%) cervical

Table 3. GROUP A—ADJUVANT THERAPY AND SURGERY

	Group 1	Group 2	Group 3
	No Tumor	Microscopic Tumor	Gross Tumor
Number	14 (32%)	15 (34%)	15 (34%)
Alive	9	9	9
Adenocarcinoma	5	4	
Squamous	4	5	
Alive > 12 mo	6	6	2
Adenocarcinoma	3	3	
Squamous	3	3	
Years of survival	3, 3, 3.5, 6.5, 9.0, 9.0	1.5, 2.5, 2.5, 2.5, 3.0, 4.5	2.0, 2.5

Tumor downsizing—44 patients.

esophageal fistulas after transhiatal esophagectomy. All resolved spontaneously from 2 to 12 days postoperatively, and none resulted in sepsis. Two occurred in group A patients, and three occurred in group B patients (surgery without adjuvant therapy). There were no local recurrences after esophagogastrectomy. There was one anastomotic reoccurrence and one recurrence in the mid stomach at the surgical TA90 staple line in the patients undergoing transhiatal esophagectomy. Five cervical strictures occurred, requiring postoperative dilatation in the THE group. Eighty-six percent of all postsurgical patients were discharged tolerating a regular diet. Fourteen percent of patients necessitated supplemental jejunal feedings at home after discharge. Transient hoarseness occurred in 6 of 70 THE patients, with an additional patient being permanently hoarse from recurrent nerve trauma.

Downstaging

Of the 44 patients who underwent preoperative chemotherapy and/or radiation, 14 (32%) downstaged to pathologic complete response (no tumor in the specimen). Fifteen of 44 (34%) had one or several microscopic foci of residual tumor within the wall of the esophagus. The remaining 15 (34%) had residual gross tumor in the esophagus. Overall, 29 of 44 patients (66%) had a major clinical response with no gross tumor visualized at the preoperative endoscopy, with biopsies demonstrating only fibrosis or ulceration. The number of patients alive to date and those with survival beyond 12 months are listed in Table 3. Nine of 14 (64%) and 9 of 15 (66%) patients are alive in the downstaged pathologic complete response and microscopic tumor groups, respectively. Six of the patients in each group are beyond 12 months. The number of long-term survivors in the complete response group are as follows: 3 years (2), 3.5 years (1), 6.5 years (1), and 9 years (2). Patients surviving beyond 1 year in the residual tumor (microscopic) group are alive at 1.5 years (1), 2.5 years (3), 3 years (1), and 4.5 years (1). Two patients in the residual gross tumor group are alive at 2 and 2.5 years. Seven patients remain at risk, surviving less than 12 months. There is an equal distribution of adenocarcinoma and squamous-cell carcinoma in the surviving patients in the "no tumor" and "microscopic tumor" groups. The preoperative tumor size in the two major downstaged groups are shown in Figure 3. Retrospectively there was a trend toward a slightly larger tumor size in the group that downstaged to microscopic residual tumor.

Survival

Table 4 lists the cumulative survival in major subgroups. The 1-, 3-, and 5-year cumulative survival in

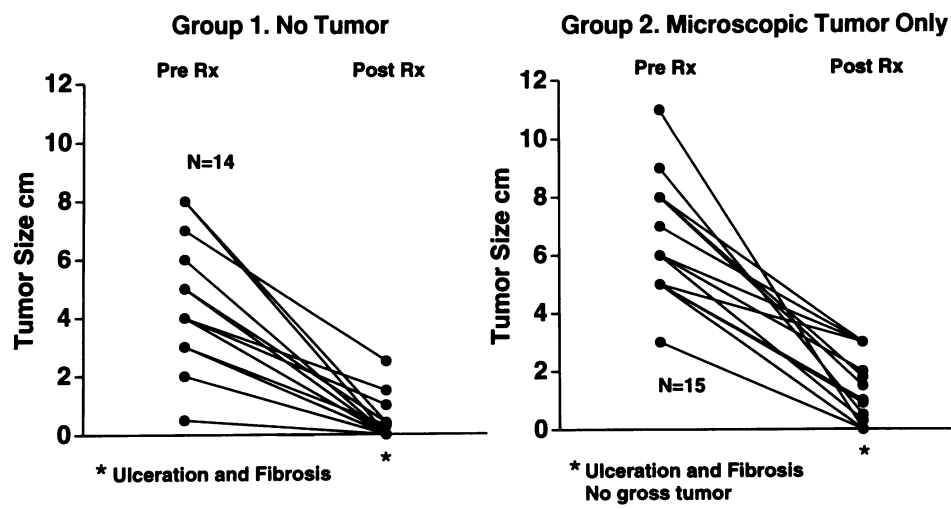

Figure 3. Preoperative tumor size in centimeters in patients who downstaged to 1) no residual tumor in the specimen (pathologic complete response) and 2) residual microscopic tumor. Post-treatment size refers to endoscopically visualized ulceration and/or fibrosis.

Table 4. SURVIVAL

Type	1 Yr	3 Yr	5 Yr
Adjuvant radiation and surgery	65%	36%	36%*
Lymph node +	44%	—	
Lymph node −	73%	49%	49%†
No adjuvant radiation (surgery only)	32%	18%	11%*
Lymph node +	15%	8%	4%‡
Lymph node −	52%	30%	20%‡
Downstage groups			
No tumor	76%	57%	57%
Microscopic tumor	77%	31%	—
Gross tumor			

* p = 0.04.
† p = 0.05.
‡ p = 0.09.

group A patients who underwent preoperative adjuvant therapy and surgery was 65%, 36%, and 36%, respectively. This was compared with group B patients (surgery only), whose survival was 32%, 18%, and 11% at 1, 3, and 5 years (p = 0.04) (Fig. 4). Figure 5 compares lymph node-positive and lymph node-negative group A patients, demonstrating a highly significant (p = 0.005) difference in survival. Figure 6 demonstrates survival by lymph node status in group B patients undergoing surgery without adjuvant therapy. Five-year survival was 20% and 4%, respectively, in lymph node-negative and positive patients (p = 0.09). Cumulative survival in patients downstaged after preoperative adjuvant therapy is shown in Figure 7. There currently is no significant difference in the "no tumor" and "microscopic tumor" groups. Actuarial survival at 1 and 3 years is 76% and 57% in group 1 and 77% and 31% in the residual microscopic tumor group (group 2), respectively. There was a trend toward increased survival in patients undergoing preoperative radiation and chemotherapy compared

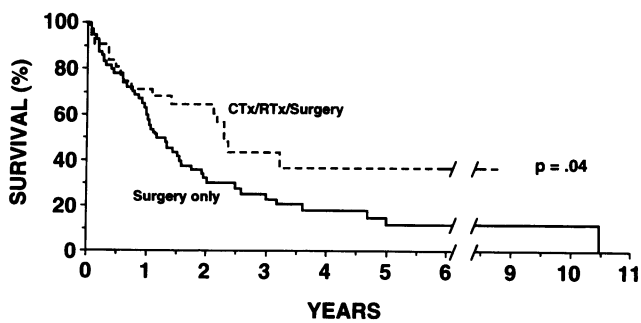

Figure 4. Survival in the 44 patients who underwent adjuvant therapy and surgery compared with the 54 patients with only surgical resection. Cumulative 5-year survival was 36% and 11%, respectively.

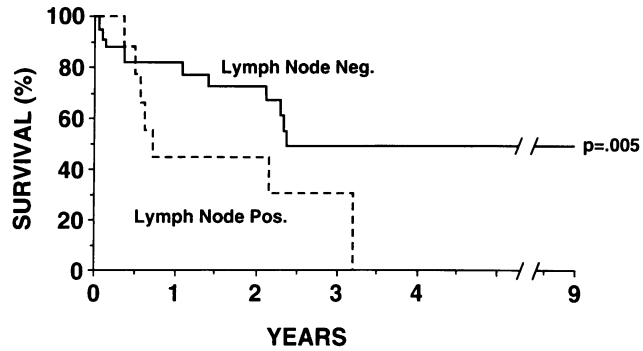

Figure 5. Survival in lymph node-negative *versus* lymph node-positive patients in the adjuvant therapy and surgery group (44 patients).

with those receiving radiation therapy only, but this did not achieve significance. Five-year survival was 44% and 18% in the combined chemoradiation group and radiation-only group, respectively (Fig. 8). Figure 9 demonstrates the survival in those unresectable patients undergoing either preoperative adjuvant therapy or surgery only. Chemoradiation had no positive effect on survival in this unfortunate group.

Lymph Node Status

Ten of the 44 patients who underwent preoperative adjuvant therapy and surgery had positive lymph nodes (23%). This was compared with the "surgery only" group (B) who demonstrated positive lymph node pathology in 26 of 54 patients (48%). Pretreatment with either radiation or chemotherapy resulted in a significant decrease by more than half the number of lymph nodes seen in the "surgery only" group (p = 0.02). The lymph node status in groups A and B and the three downstaged subgroups are listed in Table 5. Twenty-eight of the 29 patients who had a major clinical downstaging response to preoperative adjuvant therapy had negative lymph nodes. Of the ten lymph node-positive patients in the ad-

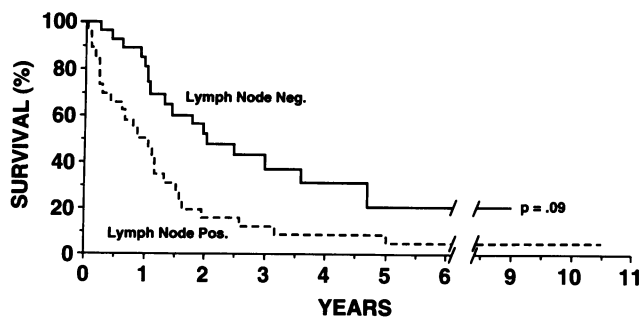

Figure 6. Survival and lymph node status in patients who underwent surgery without adjuvant therapy (54 patients.)

Table 5. LYMPH NODE STATUS

Group	No	Positive Nodes	Percent
Adjuvant Rx & surgery	44	10	23%*
Surgery only	54	26	48%
Downstage			
No tumor	14	0	0%
Microscopic tumor	15	1	6.6%
Gross tumor	15	9	60%

* p = 0.02.

juvant therapy group, nine were group 3 patients with residual gross tumor in the resected specimen.

DISCUSSION

In this retrospective, nonrandomized review, we found a significant survival advantage in those patients undergoing preoperative radiation and/or chemotherapy compared with patients undergoing only surgical resection. Increased survival seemed to correlate with both major downstaging groups—pathologic complete response and microscopic tumor only. The lymph node status was negative in 28 of 29 patients, comprising both of these downstaged groups. Although our study was nonrandomized, we believe that it is unlikely that these were random events with inadvertent selection. Although difficult to prove, we believe that it is likely that combined chemoradiation sterilized at least some—if not most—of the lymph nodes in these downstaged groups.

Historically, squamous-cell carcinoma has been considered most responsive to radiotherapy or chemoradiation. The addition of adenocarcinoma to the previously responsive epidermoid carcinoma is now well established. Sauter et al. reported a 23% complete response

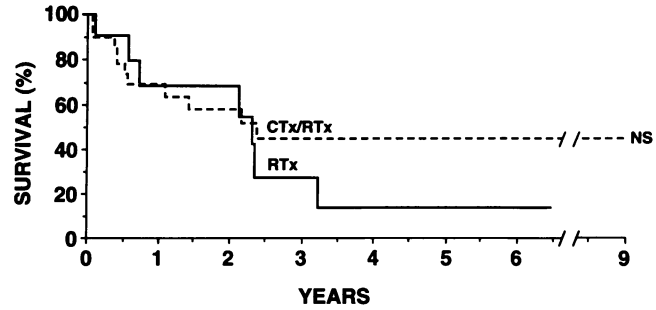

Figure 8. Survival in 35 patients who underwent preoperative chemotherapy and radiation compared with 17 patients with preoperative radiation therapy only. No current significance differences,but a trend toward increased survival with combined therapy.

rate in patients with adenocarcinoma, although long-term survival remains in question.[9] Forastiere, however, documented a 5-year survival of 34% and 31% in adenocarcinoma and squamous-cell patients, respectively, with median survival durations of 32 and 23 months.[11] In subdividing their groups to "potentially curable" resections, they increased 5-year survival rates to 36% and 43% for adenocarcinoma and squamous-cell patients with median survival of 32 and 44 months. Long-term survivors in our study had equal distribution between the two major tumor types.

In our study, there were two major downstaged groups that had what we term a major clinical response. In 29 of 44 patients (66%), preoperative endoscopy failed to identify gross esophageal tumor, and biopsies demonstrated only fibrosis or ulcerations. More extensive biopsies may have demonstrated tumor, but this approach may be too impractical and time consuming, and may yield no other positive results than restratifying patients. Although our follow-up was shorter, overall survival in our pathologic complete response group was similar to that reported by the Michigan group.[10,11] Their residual tumor group may be similar to our second downstaged

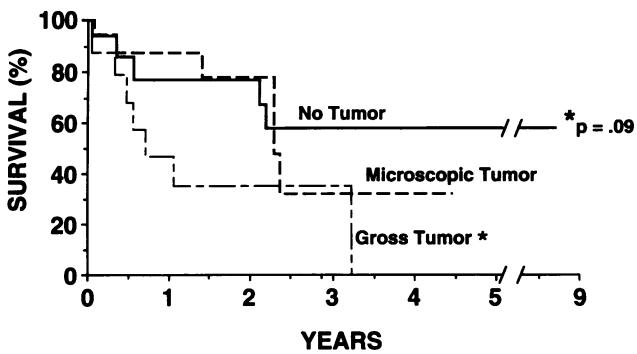

Figure 7. Survival in the downstaged groups after preoperative adjuvant therapy. Cumulative 3- and 5-year survival of 57% in the group without tumors. Eighteen of 29 patients in groups 1 and 2 are alive to date.

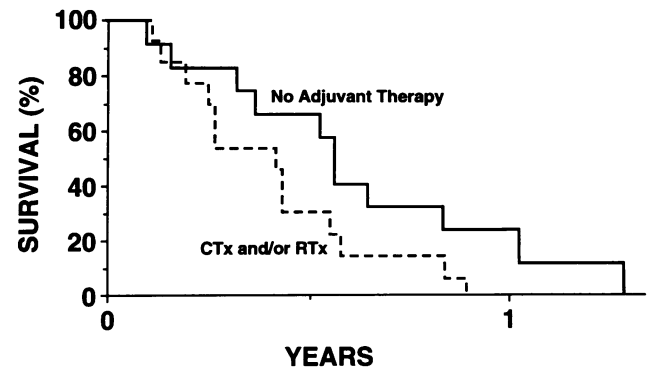

Figure 9. Survival in unresectable patients with either no adjuvant therapy or chemotherapy and/or radiation (NS).

group, in which small microscopic foci were seen within the wall of the esophagus. This group also contained most of the remaining lymph node-negative patients with 3-year survival of 31% to date. Although the numbers are small, this study demonstrates that if a break point for surgery *versus* no surgery were to occur, it might be after the findings of routine preoperative endoscopy. The group that had gross identifiable tumor at preoperative endoscopy, had an overall poor prognosis, although two patients have survived 2 and 2.5 years to date. Certainly these data suggest that most, if not all, of the patients with a major clinical response to preoperative chemoradiation should undergo surgical resection. The long-term survival in the residual tumor group reported by the Michigan group and the 60% 5-year survival in their complete response group support the concept that combined chemoradiation should precede surgery and not be considered primary therapy except in specific circumstances, such as high-risk patients or others who are not surgical candidates. Modifications in radiation dosage or future changes in chemotherapeutic agents may alter this approach.

We documented a trend toward increased survival in the chemoradiation group compared with those patients receiving radiation therapy only. Because of small numbers, overall survival failed to achieve statistical significance. Based on our results and those reported by others, we doubt that we will be offering preoperative radiation only, except in specific circumstances of palliation or inability to tolerate chemotherapy.[17,18] In this study, only five patients received preoperative chemotherapy without radiation. One patient downstaged to complete pathologic response, but our numbers are too small to corroborate chemotherapy survival reported by others.[12,19] Preoperative chemoradiation resulted in minimal toxicity, in this study, at the standard doses used. However, this is in contrast to fairly high morbidity and toxicity reported by others after varying regimens of chemotherapy or high-dose radiation.[9,12,20,21]

We believe that a standard regimen of preoperative chemoradiation results in significant downstaging, increased survival, and the possibility of local and regional lymph node sterilization. Currently, we continue to offer this protocol to all patients with either adenocarcinoma or squamous-cell carcinoma of the esophagus in any location. However, with the more modern technology of spiral CT, we have begun to prospectively evaluate preoperative lymph node status using this modality and endoscopic ultrasound in selected patients. Whether this approach will alter survival or obviate the necessity of surgery in selected groups of patients remains in question.

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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