Prognostic Factors After Combined Modality Treatment of Squamous Cell Carcinoma of the Esophagus

Nabil P. Rizk, MD, Venkatraman E. Seshan, PhD,¶ Manjit S. Bains, MD,* David H. Ilson, MD,† Bruce D. Minsky, MD,‡ Laura Tang, MD,‖ and Valerie W. Rusch, MD**

Introduction: In a previous study of prognostic factors in patients with loco-regionally advanced adenocarcinoma of the esophagus treated with chemo-radiotherapy (CRT) followed by resection, we found that residual nodal disease was most prognostic of outcome. In this study, we evaluated prognostic factors among patients with squamous cell carcinoma (SCC) of the esophagus who have undergone a similar treatment regimen.

Methods: A retrospective review of patients with SCC of the esophagus who received CRT before esophagectomy. Data collected included demographics, CRT details, pathologic findings, and survival. Statistical methods included recursive partitioning and Kaplan-Meier analyses.

Results: From 1996 to 2006, 91 patients were appropriate for this analysis. Complete pathologic response in the primary tumor (pt-pCR) occurred in 49 patients (53.8%), including 10 of 91 (10.9%) who had a pt-pCR but residual nodal disease. Recursive partitioning analysis identified three prognostic groups: (1) group 1 ($n = 52$), patients with minimal residual local disease (pt-pCR and T1-N any); (2) group 2 ($n = 28$), patients with residual T2 disease (N0 and N1) and patients with T3-4N0 disease; and (3) group 3 ($n = 11$), patients with residual T3-4N1 disease. Three-year survival was 68.4% in group 1, 45.6% in group 2, and 0 % in group 3 ($p < 0.001$).

Conclusions: Unlike adenocarcinoma, in which residual nodal disease after CRT is the most significant predictor of survival, in SCC of the esophagus, pt-pCR or minimal residual local disease after CRT predicts the best survival. These findings aid the design of future clinical trials.

Key Words: Esophageal squamous cell cancer, Chemoradiation, Prognostic variables.

(*J Thorac Oncol.* 2007;2: 1117–1123)

Most studies of induction therapy followed by surgery for the treatment of loco-regionally advanced esophageal cancer do not distinguish among tumor histologic types and their potential dissimilarities in response to treatment or posttreatment prognostic factors. Published data suggest that esophageal squamous cell carcinomas (SCC) may respond differently to induction chemoradiotherapy (CRT) than esophageal adenocarcinomas,[1–3] especially with respect to the likelihood of a complete pathologic response (pCR). pCR is commonly used to measure treatment response and is often associated with improved survival relative to patients who have residual disease.[4] Although the frequency of pCR is difficult to compare among studies for various reasons, including the lack of distinction between tumor histologies, varying radiation doses, and different pretreatment clinical stage, pCR rates in adenocarcinoma are generally in the range of 20% to 30%, whereas in SCC, pCR occurs in up to 50% of patients.[3–8] Whereas a pCR is commonly associated with improved survival,[2,8–11] this difference in pCR rates does not seem to translate into better overall outcomes in SCC after CRT in most studies.[1,12–15] This discrepancy raises the possibility that additional factors influence survival in these two tumor histologies.

We recently reported our analysis of prognostic factors among patients with adenocarcinoma of the esophagus undergoing CRT and surgery.[16] Results from that analysis showed that after CRT, AJCC tumor stage did not predict survival accurately, that residual nodal disease was the most important prognostic factor, and that the presence of residual primary tumor had less influence on survival. Other studies corroborate our findings.[17] In the current study, we perform a similar analysis among patients with SCC of the esophagus to identify important prognostic factors that might be used as end points in selecting patients for resection and in designing future clinical trials.

METHODS

Acquisition of Clinical Data

We undertook a retrospective review of all patients undergoing resection for SCC of the esophagus at Memorial Sloan-Kettering Cancer Center between January 1996 and February 2006. January 1996 is when an institutional electronic medical record system was instituted and is therefore a time from which highly reliable data can be obtained. Patients who did not have survival information available were excluded from this analysis. We also excluded any patient who did not undergo preoperative chemotherapy with radiation or

Departments of *Surgery, †Medicine, ‡Radiation Oncology, and ‖Pathology, Memorial Sloan Kettering Cancer Center; and ¶Biostatistics Core, Columbia University, New York, New York.

Disclosure: The authors declare no conflict of interest.

Address for correspondence: Nabil P. Rizk, MD, Thoracic Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, Room C-883, New York, NY 10021. E-mail: rizkn@mskcc.org

ISSN: 1556-0864/07/0212-1117

who received definitive nonsurgical treatment but eventually underwent surgery as salvage therapy.

The data collected included patient age, preoperative clinical stage (based on a combination of radiographic and endoscopic studies), type of preoperative therapy (type of chemotherapy, amount of radiation, length of time from the completion of radiation to surgery), depth of tumor invasion, estimated treatment effect, and the number of all malignant and benign lymph nodes. Overall survival, as calculated from the time of operation, was obtained from the electronic records at Memorial Sloan-Kettering Cancer Center and confirmed from the Social Security Death Index. June 1, 2006, was the censoring date for survival.

Clinical Stage

Patients treated with preoperative chemoradiotherapy at our institution are all deemed to have loco-regionally advanced disease. Confirmation of clinical stage was obtained with a combination of computed tomography (CT), positron emission tomography (PET), and endoscopic ultrasound (EUS). Evidence of lymph node involvement by CT, PET, or EUS and evidence of a T3 lesion by EUS were used to confirm T3, N1, or M1a or some combination of these T, N, M stages (stages IIa to IVa).

TNM Classification

The T, N, and M descriptors and staging classification used for this analysis were those defined in the sixth edition of the *AJCC Cancer Staging Manual*.[18] Because of some variations in the nomenclature used by surgeons and pathologists in identifying the exact location of lymph nodes within a resected specimen, lymph nodes were consistently identified as "celiac axis" if they were labeled as left gastric, splenic, celiac, or hepatic. Within the chest, lymph nodes were identified as subcarinal lymph nodes if they were labeled as either level 7, left mainstem, or right mainstem. M1a nodes were labeled according to the primary tumor location. Celiac axis nodes were M1a for distal esophageal, gastroesophageal junction, and gastric cardia tumors that involved the gastroesophageal junction. Cervical lymph nodes were M1a for tumors of the proximal third of the esophagus. The total number of involved lymph nodes included any positive lymph node found excluding remote nodes that would be assigned as M1b. The overall number of lymph nodes included the sum of all malignant and benign lymph nodes found. Disease was considered M1b if nodes were positive outside the regional basin or if visceral metastases were identified. The depth of primary tumor invasion was assigned as described in the AJCC staging manual. A complete response was considered to have occurred when no evidence of viable tumor was noted (i.e., T0N0). Patients with T0N1 disease were categorized as having stage IIb disease. In the analyses that used the number of involved lymph nodes as variables, the nomenclature used to distinguish this from the AJCC nodal system is N($\#^+$).

Estimation of Pathologic Complete Response

The gross appearance of treated tumors varied from mucosal ulceration to a fibrous scar, or a prominent mass lesion in the case of a less than profound tumor regression. Photographs of the gross specimen were taken for all cases. The ulcerated or the scarred gross lesion at gastroesophageal junction was blocked, sequentially and entirely submitted for histopathological evaluation. When the tumor was large in size (>5.0 cm), only representative sections of the tumor were examined microscopically. At the microscopic level, a positive treatment related-effect was observed as abolition of the malignant epithelium and replacement by reactive fibrosis or fibro-inflammation within the mucosa or the gastroesophageal wall. The ultimate pathological response to treatment was thus determined by the amount of residual viable carcinoma in relation to areas of fibrosis or fibro-inflammation within the gross lesion, which was inversely associated with, and expressed as percentage of, a favorable treatment response. Thus, a 100% treatment response indicated fibrosis or fibro-inflammation within an entire gross lesion without microscopic evidence of carcinoma. A pCR was assigned when there was both a 100% local treatment response and no evidence of residual nodal involvement. A pCR in the primary tumor (pt-pCR) was assigned when there was a 100% treatment response in the primary tumor but evidence of residual viable nodal disease.

Statistical Analysis

Patient characteristics are described using tables for categorical data and medians and range for continuous variables. Survival time was measured from the date of surgery to the date of death or last follow-up. Survival curves were estimated using the Kaplan-Meier method. Maximal log rank analysis[19] was used to determine the optimal cutoffs for lymph node numbers. Recursive partitioning[20] was used to develop a scheme to classify patients into stage categories. We used recursive partitioning modeling because the goal of a staging system is to group the patients into homogenous categories with respect to their prognosis (in this case, survival). Because several clinical characteristics (T, N, M, lymph node numbers) affect the prognosis of a patient, using traditional multivariable modeling such as Cox proportional hazards regression to account for these covariates does not provide a simple way to group the patients by prognosis categories. Recursive partitioning, however, partitions patients recursively at each step into two groups based on the covariate that gives the maximal separation with respect to their prognosis. In addition to providing an algorithm by which to group the patients into categories, it accounts for interactions among factors. Thus, recursive partitioning was used to develop a scheme to classify patients into stage categories. Recursive partitioning was performed using the RPART routines of Therneau and Atkinson.[21] This algorithm partitions after scaling the survival times so as to fit an exponential model and the hazard rate in the "exponential-scaled" times of terminal nodes are reported.

RESULTS

Clinical Data

During the study period, 856 esophagectomies were performed, and 91 patients were appropriate for this analysis.

One patient meeting the analysis criteria was excluded because of lack of survival information. Ten patients were excluded because they underwent a palliative esophagectomy. Early clinical stage disease or other tumor type caused 401 patients to be excluded. Sixty patients were excluded because they received preoperative chemotherapy only under a previous protocol. The rest who were excluded ($n = 393$) all had adenocarcinoma and underwent preoperative chemoradiation. The median patient age was 62.1 years (range, 22.3–79.7 yr), and 35 patients were female (38.5%). Of the 91 patients included, 78 patients who received preoperative radiotherapy had adequate treatment information. Sixty-three (80.8%) were treated with a total dose of 5040 cGy (180 cGy daily in 28 fractions). Most patients ($n = 85$, 93.4%) received various concurrent cisplatin-based chemotherapy regimens, according to sequential clinical trials performed during this time frame (Tables 1 and 2).[22]

Outcome in Patients with a Pathologic Complete Response to Induction Therapy

The R0 resection rate was 93.4%. Overall, 49 of 91 patients (53.8%) had evidence of a pt-pCR. Of these 49 patients, 10 had persistent nodal involvement; thus, 39 patients had a pCR (42.8%). The survival of patients with a pt-pCR was significantly better ($p < 0.01$) than that of patients with residual disease in the primary tumor (3-year survival of 68.5 vs 39.0 months, respectively). Although the number of patients analyzed is small, the involvement of lymph nodes in patients with a pt-pCR ($n = 10$) does not seem to influence survival compared with patients who had a pCR ($n = 39$) ($p = 0.45$) (Figure 1).

TABLE 1. Patient Characteristics

Characteristic	Patients (*n*)	%
Total	91	
Sex (F)	35	38.5
Age (yr)	62.1 (22.3–79.5)	
Staging		
CT scan	91	100
PET (pre-, post-, or both)	69	75.8
EUS	53	58.2
RT dose (Gy)	50.40 (27–60)	
Time from RT to surgery (days)	56.5 (11–188)	
Chemotherapy		
Cisplatin-paclitaxel	45	49.5
Cisplatin-irinotecan	20	22.0
Cisplatin-5 fluorouracil	13	14.3
Other	13	14.3
Procedure type		
McKeown	23	25.2
Ivor Lewis	55	60.4
Transhiatal	13	14.3
Tumor location		
Proximal third	9	9.9
Middle third	33	36.3
Distal third	49	53.8

Data are expressed as *n* or median (range). RT, radiation.

TABLE 2. Pathologic Stage in Relationship to Treatment Response and Prognostic Group Categories

Patients	T	N	AJCC Stage	pt-pCR*	% Tx Response	Prognostic Group[a]
39	0	0	0	Yes	100	1
9		1	IIb	Yes	100	1
2	is	0	0	Yes	95	1
0		1	IIb	[b]	[b]	[b]
2	1	0	I	No	96.5	1
0		1	IIb	[b]	[b]	[b]
8	2	0	IIa	No	74.4	2
5		1	IIb	No	62.8	2
15	3	0	IIb	No	27.3	3
9		1	III	No	20.7	3
0	4	0	IIb	[b]	[b]	[b]
2		1	III	No	5	3

pt-pCR, Pathologic complete response in the primary tumor.
[a]Based on recursive partitioning analysis.
[b]No patients in group.
Tx, Treatment.

Recursive Partitioning Analysis of T, N, M

Recursive partitioning, using T, N, and M as variables, indicates that the principal determinant of improved survival is the presence of either a pt-pCR or of minimal residual local disease (T1 disease or less) (Figure 2). This group (group 1) is primarily composed of patients with a local pCR (pCR regardless of nodal status), with an additional smaller subset of patients consisting of two patients with carcinoma in situ and two patients with T1 disease. Of note, there were no TisN1 or T1N1 patients. The next prognostic group (group 2) is composed of patients with T2 disease regardless of nodal status and of patients with T3N0 disease. The worst prognostic group (group 3) showed minimal evidence of local treatment response and consisted of patients with T3N1 and T4N1 disease. Notably, these three prognostic groups all had similar clinical stages before treatment (Table 3).

Percent Treatment Response

Within the three prognostic groups identified in the recursive partitioning analysis, the estimated treatment response was best in group 1 and least in group 3 (Table 3). Of note, there was no statistical correlation between nodal status and treatment response in the primary tumor. Posttreatment node-negative patients had a mean treatment response in the primary tumor of 81.2%, and posttreatment node-positive patients had a mean treatment response in the primary tumor of 63.7% ($p = 0.07$).

Impact of Positive Lymph Nodes

Emphasizing the fact that the presence of residual nodal disease has a minor impact on survival in SCC of the esophagus after CRT, an analysis of survival based on the number of positive lymph nodes shows that within the range of zero to four involved nodes, survival is not appreciably

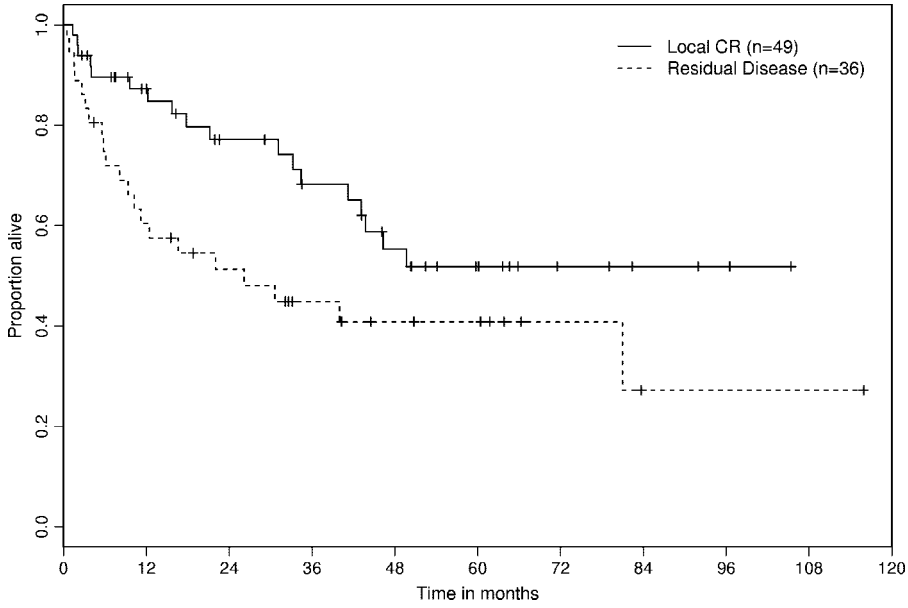

FIGURE 1. Survival of patients with a local pathologic complete response (pCR) compared with residual disease (pt-pCR).

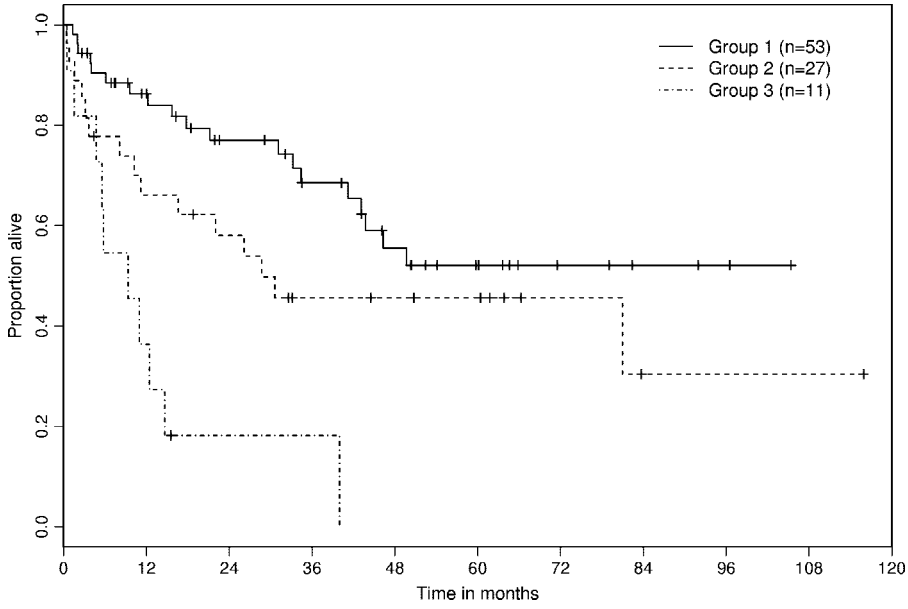

FIGURE 2. Recursive partitioning using T, N, M as variables.

TABLE 3. Prognostic Group Characteristics

Group	Mean Tx Effect (%)	3-yr Survival (%)	5-yr Survival (%)
1 (n = 52)	99.7	68.4	52.0
2 (n = 28)	48.6	45.6	45.6
3 (n = 11)	18.8	18.2	0.0

Tx, Treatment.

different (Figure 3). Patients with five or more positive nodes do worse, although there were few patients in this group (n = 5). When the patients who had metastases in five or more nodes are excluded from the analysis, survival is the same regardless of whether nodes are positive (p = 0.26, figure not shown).

DISCUSSION

Our recently published results on the prognostic characteristics of adenocarcinoma of the esophagus after CRT indicated that nodal status rather than overall TNM stage was the most important predictor of survival and that the depth of the residual primary tumor (T stage) was much less predictive of outcome. In addition, this analysis found that only 20% of patients with adenocarcinoma had a pCR after treatment.[16] In the current study, we showed that SCC of the esophagus has different post-CRT prognostic characteristics than adenocarcinoma. We found that the most important prognostic factor after CRT is the presence of minimal residual local disease. Nodal status seems to have minimal influence on outcome, although the number of

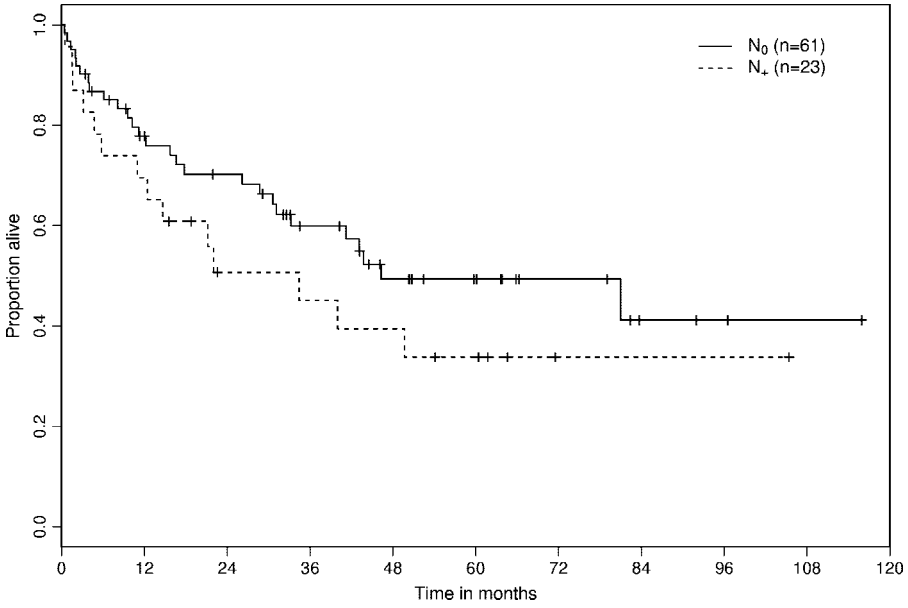

FIGURE 3. Survival of patients relative to number of positive lymph nodes.

patients is too small to draw any firm conclusions. This group of patients represents 57.1% of treated patients, most of whom have had a pt-PCR, and all of whom have evidence of a significant treatment response (mean 99.7%). The 3-year and 5-year survivals of this group of patients are highly favorable at 68% and 52%, respectively. In contrast, the worst prognostic group showed minimal evidence of local treatment response and included T3N1 and T4N1 tumors. This subset of patients had a mean estimated treatment response of only 18.7%. Median survival of these patients was only 9.4 months, and all patients were dead by 40 months.

TABLE 4. Summary of Studies of Combined Modality Therapy for Esophageal Carcinoma

Studies Including Both Adeno and Squamous Cell Carcinoma				
Author	**Histology**	**Radiation Dose (Gy)**	**Chemotherapy**	**pCR (%)**
Burmeister et al.[3]	SCC (80) ADA (45)	35	C, F	228
Schneider et al.[8]	SCC (46) ADA (28)	36	C, F	1815
Slater et al.[5]	SCC (7) ADA (26)	40	C, F	438
De Vita et al.[6]	SCC (26) ADA (13)	40	C, F	350
Stahl et al.[7]	SCC (43) ADA (9)	40	C, F, E, L	51 22
Wolfe et al.[11]	SCC (72) ADA (93)	45	C, VC, F	40 20
Adelstein et al.[12]	SCC (24) ADA (48)	45	C, F	36 22
Jones et al.[13]	SCC (39) ADA (15)	45	C, F	43 33
Studies including only one tumor histology				
Le Prise et al.[27]	SCC (41)	20	C, F	10
Seydel et al.[28]	SCC (41)	30	C, F	30
Bosset et al.[25]	SCC (112)	37	C	26
Walsh et al.[29]	ADA (113)	40	C, F	25
Donington et al.[4]	ADA (47)	45	C, F	26
Rizk et al.[16]	ADA (240)	50.4	C, F or C, CPT11 or C, paclitaxel	20
Current study	SCC (91)	50.4	C, F, or C, CPT11 or C, paclitaxel	53.8

C, cisplatin; F, 5-fluorouracil; L, leucovorin; V, vincristine; CPT11, irinotecan; P, paclitaxel.

Interestingly, the published literature rarely makes a distinction between SCC and adenocarcinoma of the esophagus, usually combining these two tumor types in retrospective analyses and in clinical trials, despite the fact that the etiology of these two diseases is clearly recognized as different,[3] and that the management of SCC in other sites of the digestive tract such as head and neck[23] and anal SCC[24] is primarily chemoradiotherapy without resection. For these patients, surgery is used only as salvage therapy. In the five major prospective randomized clinical trials comparing CRT with surgery alone for esophageal cancer, three were done for SCC only, one for adenocarcinoma only, and two for patients with both tumor types. This distribution of tumor type was primarily a reflection of the predominant disease patterns at the time of the study rather than from any conscious recognition of differences between the two histologies. Among the studies that examined only SCC,[25–27] all used suboptimal radiation doses, and two studies treated patients with sequential rather than concurrent chemoradiation, making the results of these studies difficult to interpret within the context of current chemoradiation protocols. The two trials that included both tumor histologies show results similar to ours. In the report by Urba et al.,[2] no explicit data are provided regarding responses to treatment by tumor histology, but mention is made of the fact that in an earlier trial,[9] in which a larger proportion of patients had SCC (25% vs. 51%), patients treated with CRT did relatively better than in the current trial, suggesting that SCC might be more responsive to treatment. In a trial reported by Burmeister et al., the investigators noted a higher incidence of pCR in SCC, as well as a survival benefit of CRT in SCC but not in adenocarcinoma. The authors suggest that perhaps the vigorous response of SCC to CRT explains why clinical trials have found similar survival outcomes in patients undergoing CRT plus surgery compared with CRT alone.[3]

The focus of many retrospective studies in evaluating pathologic response to CRT has been the attribution of posttreatment pCR as a marker of better prognosis. The reported pCR rates in the literature vary widely but are generally higher in patients who receive higher radiation doses and in patients with SCC (Table 4). The difference in pCR rates between SCC and adenocarcinoma is more obvious in studies that use higher radiation doses (Table 4). In our study, all patients had loco-regionally advanced disease, and all had similar doses of radiation. Furthermore, the radiation dose was similar to that commonly given when CRT is used as definitive treatment.

The literature is similarly inconsistent in its findings on the benefits of achieving a pCR. Specifically, some studies indicate that a pCR correlates with better survival,[2,8,9,11] whereas others do not.[10] Some of this variability may be related to the various proportions of tumor histologies and pretreatment stages in these studies, as well as different radiation doses administered. In addition, as we show in this study, rather than focusing only at pCR rates, it seems that evaluating patients for the presence of pt-pCR or minimal residual disease in the primary tumor is a more accurate way to identify patients with a better prognosis.

The major limitation of this study is that it is a retrospective analysis of a relatively small number of patients from a single institution. Validation of these results are needed from other datasets.

In summary, our study shows that a significant subset of patients with esophageal SCC with loco-regionally advanced disease respond dramatically to what is commonly considered to be definitive chemoradiotherapy. In contrast to our previous publication on esophageal adenocarcinoma, the characteristic that identifies favorable posttreatment prognosis in SCC is a significant treatment response in the primary tumor, rather than evidence of residual nodal disease. These findings can aid in the design of future clinical trials and suggest that patients should be selected or stratified by tumor histology. In addition, given the high response to nonsurgical treatment, future randomized trials comparing CRT with CRT plus surgery may best be performed in patients with SCC rather than adenocarcinoma.

REFERENCES

1. Heath EI, Burtness BA, Heitmiller RF, et al. Phase II evaluation of preoperative chemoradiation and postoperative adjuvant chemotherapy for squamous cell and adenocarcinoma of the esophagus. *J Clin Oncol* 2000;18:868–876.
2. Urba SG, Orringer MB, Turrisi A, et al. Randomized trial of preoperative chemoradiation versus surgery alone in patients with locoregional esophageal carcinoma. *J Clin Oncol* 2001;19:305–313.
3. Burmeister BH, Smithers BM, Gebski V, et al. Surgery alone versus chemoradiotherapy followed by surgery for resectable cancer of the oesophagus: a randomised controlled phase III trial. *Lancet Oncol* 2005;6:659–668.
4. Donington JS, Miller DL, Allen MS, et al. Preoperative chemoradiation therapy does not improve early survival after esophagectomy for patients with clinical stage III adenocarcinoma of the esophagus. *Ann Thorac Surg* 2004;77:1193–1199.
5. Slater MS, Holland J, Faigel DO, et al. Does neoadjuvant chemoradiation downstage esophageal carcinoma? *Am J Surg* 2001;181:440–444.
6. De Vita F, Di Martino N, Orditura M, et al. Preoperative chemoradiotherapy for squamous cell carcinoma and adenocarcinoma of the esophagus: a phase II study. *Chest* 2002;122:1302–1308.
7. Stahl M, Wilke H, Fink U, et al. Combined preoperative chemotherapy and radiotherapy in patients with locally advanced esophageal cancer: interim analysis of a phase II trial. *J Clin Oncol* 1996;14:829–837.
8. Schneider PM, Baldus SE, Metzger R, et al. Histomorphologic tumor regression and lymph node metastases determine prognosis following neoadjuvant radiochemotherapy for esophageal cancer: implications for response classification. *Ann Surg* 2005;242:684–692.
9. Forastiere AA, Orringer MB, Perez-Tamayo C, et al. Preoperative chemoradiation followed by transhiatal esophagectomy for carcinoma of the esophagus: final report. *J Clin Oncol.* 1993;11:1118–1123.
10. Tamin WZ, Davidson RS, Quinlan RM, et al. Neoadjuvant chemoradiotherapy for esophageal cancer: is it worthwhile? *Arch Surg* 1998;133:722–726.
11. Wolfe WG, Vaughn AL, Seigler HF, et al. Survival of patients with carcinoma of the esophagus treated with combined-modality therapy. *J Thorac Cardiovasc Surg* 1993;105:749–756.
12. Adelstein DJ, Rice TW, Becker M, et al. Use of concurrent chemotherapy, accelerated fractionation radiation, and surgery for patients with esophageal carcinoma. *Cancer* 1997;80:1011–1020.
13. Jones DR, Detterbeck FC, Egan TM, et al. Induction chemoradiotherapy followed by esophagectomy in patients with carcinoma of the esophagus. *Ann Thorac Surg* 1997;64:185–192.
14. Muller JM, Erasmi H, Stelzner M. Surgical therapy of oesophageal carcinoma. *Br J Surg* 1990;77:845–857.
15. Coia LR, Engstrom PF, Paul AR, et al. Long-term results of infusional 5-FU, mitomycin-C and radiation as primary management of esophageal carcinoma. *Int J Radiat Oncol Biol Phys* 1991;20:29–36.

16. Rizk NP, Venkatraman E, Bains MS, et al. American Joint Committee on Cancer staging system does not accurately predict survival in patients receiving multimodality therapy for esophageal adenocarcinoma. *J Clin Oncol* 2007;25:507–512.
17. Dunne B, Reynolds JV, Mulligan E, et al. A pathological study of tumor regression in oesophageal adenocarcinoma treated with preoperative chemoradiotherapy. *J Clin Pathol* 2001;54:841–845.
18. American Joint Committee on Cancer. FL Greene, DL Page, ID Fleming, et al (Eds). AJCC Cancer Staging Handbook. 6th Ed. New York: Springer-Verlag, 2002.
19. Breiman L, Friedman J, Stone CJ, et al. *Classification and Regression Trees.* New York: Chapman & Hall, 1984.
20. Lausen B, Schumacher M. Maximally selected rank statistics. *Biometrics* 1992;48:73–85.
21. Therneau TM, Atkinson EJ. Section of biostatistics. In: HSR Do (Ed.). *An Introduction to Recursive Partitioning Using the RPART Routines.* Rochester, MN: Mayo Clinic, 1997.
22. Ilson DH, Minsky B, Kelsen D. Irinotecan, cisplatin, and radiation in esophageal cancer. *Oncology* 2002;16(5 Suppl 5):11–15.
23. Renaud-Salis JL, Blanc-Vincent MP, BrigPre J, et al. Epidermoid cancers of the oropharynx. *Br J Cancer* 2001;84(Suppl 2):37–41.
24. Eng C. Anal cancer: current and future methodology. *Cancer Invest* 2006;24:535–544.
25. 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;337:161–167.
26. Nygaard K, Hagen S, Hansen HS, et al. Pre-operative radiotherapy prolongs survival in operable esophageal carcinoma. A randomized, multicenter study of pre-operative radiotherapy and chemotherapy. The second Scandinavian trial in esophageal cancer. *World J Surg* 1992;16: 1104–1110.
27. Le Prise E, Etienne PL, Meunier B, et al. A randomized study of chemotherapy, radiation therapy, and surgery versus surgery for localized squamous cell carcinoma of the esophagus. *Cancer* 1994; 73:1779–1784.
28. Seydel HG, Leichman L, Byhardt R, et al. Preoperative radiation and chemotherapy for localized squamous cell carcinoma of the esophagus: a RTOG study. *Int J Radiat Oncol Biol Phys* 1988;14:33–35.
29. Walsh TN, Noonan N, Hollywood D, et al. A comparison of multimodal therapy and surgery for esopahgeal adenocarcinoma. *N Engl J Med* 1996;335:462–467.

