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ORIGINAL REPORT

Association of Activated Transcription Factor Nuclear Factor κB With Chemoradiation Resistance and Poor Outcome in Esophageal Carcinoma

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Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

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ABSTRACT

Purpose
The lack of effective treatment for localized esosphageal cancer leads to poor patient outcome. Nuclear factor κB (NF-κB), a transcriptional factor, is constitutively activated or treatment induced in esophageal cancer and may influence treatment outcomes.

Patients and Methods
Pre- and post-treatment cancer specimens from patients enrolled onto a clinical trial were studied for the expression of activated NF-κB protein and it was correlated with histologic features, pathologic response, metastatic potential, overall survival (OS), and disease-free survival (DFS).

Results
Forty-three patients undergoing the same therapy on a protocol were studied. Twenty-one (72%) of 29 patients achieving less than complete pathologic response (pathCR) had NF-κB positive cancer, but only one (7%) of 14 patients achieving pathCR had NF-κB positive cancer ($P = < .001$). Activated NF-κB was significantly associated with aggressive pathologic features such as perineural, lymphatic, and/or vascular invasion ($P = .0004$). Eight (38%) of 21 NF-κB positive patients developed metastases compared to none of 22 NF-κB negative patients ($P = .001$). At a median follow-up of 23 months, 10 (48%) of 21 NF-κB positive patients had died compared to only one (5%) of 22 NF-κB negative patients ($P = .0013$). Observations were similar for DFS ($P = .0006$). In a multivariate model (using baseline stage, pathCR or less than pathCR, age, presence of metastatic lymph nodes in the surgical specimen, and NF-κB expression) NF-κB activation was the only independent predictor of DFS ($P = .010$) and OS ($P = .015$).

Conclusion
Our data suggest that esophageal cancers with activated NF-κB have aggressive clinical biology and poor treatment outcome. Additional understanding of NF-κB regulated pathways may uncover potential therapeutic targets.

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INTRODUCTION

Carcinoma of the esophagus or gastroesophageal junction remains one of the most virulent malignancies with a 5-year survival rate less than 20%.[1] Although surgery as primary therapy is an option for patients with locoregional (stages II and III) carcinoma, preoperative chemoradiotherapy is frequently used, despite equivocal results from randomized trials.[2-9] Preoperative chemoradiotherapy is associated with considerable morbidity and benefits only a few patients. The survival of patients who have no cancer cells in the resected specimen (pathologic complete response [pathCR]) is better than those who have chemoradiotherapy resistant cancer (less than pathCR), but the fraction of pathCR patients is approximately 27%.[10-12]

The main obstacles in the treatment of localized carcinoma of the esophagus are our inability to select optimum therapy, overcome chemoradiotherapy resistance, and prevent metastatic progression. In terms of selection of optimum therapy, there are no pretreatment clinical parameters such as age, sex, T or N stage, histology, or location of the primary cancer that can reliably predict the outcome from preoperative chemoradiotherapy.[13,14] Similarly, pretreatment molecular markers have not predicted outcome from preoperative chemoradiotherapy.[15] In addition,

the clinical biology of localized esophageal cancer treated with preoperative chemoradiotherapy suggests that chemoradiotherapy-resistant cancers tend to have metastatic progression.[16] Exploration of novel molecular markers or pathways might be of value in identifying therapeutic targets.

The transcription factor nuclear factor κB (NF-κB) is a gatekeeper of critical biologic functions, including cell survival, proliferation, and migration.[17] Mammalian NF-κB correspond to a family of five members, sharing *N*-terminal Rel homology DNA binding domain.[18] Through the Rel domain, NF-κB binds to specific DNA sequences and initiates transcription of its target genes.[18] Under normal conditions, inactive NF-κB resides in the cytoplasm as a heterotrimer of p65, p50, and IKB-α. On stimulation (ie, cytokines, viruses, growth factors, DNA damaging agents), the p65-p50 heterodimer dissociates from IKB-α, translocates to the nucleus, and binds to DNA.[17,18] Aberrant NF-κB activation (ie, constitutive or persistent nuclear localization) has been associated with inflammatory disorders and cancer.[19-21]

To potentially identify molecular signatures that are predictive of the outcome of chemoradiotherapy, we conducted gene expression profiling in a limited number of patients.[21a] Using the Ingenuity Pathway software (Ingenuity Systems, Redwood City, CA) we identified the NF-κB canonical signaling pathway as differentially expressed between cancers and normal tissue.[22-23] In addition, resistant cancers had a significantly higher expression of key regulating genes in the pathways, including TRAF2, an inhibitor of NF-κB kinase, and RelB.[17-18] However, the significance of NF-κB expression as a prognostic factor for response to preoperative chemoradiotherapy is of great interest since its inhibitors have entered clinical trials.[24-26] To better understand the cellular mechanisms underlying response to chemoradiotherapy, we determined NF-κB protein expression levels and correlated it with response and patient outcome.

PATIENTS AND METHODS

Patient Selection and Evaluation

All patients in this article participated in a clinical trial. Patients with localized, histologically-confirmed adenocarcinoma or squamous cell carcinoma of the thoracic esophagus were eligible and evaluated by computed tomography (chest and abdomen), upper gastrointestinal barium radiographs, an esophago-gastro-duodenoscopy with endoscopic ultrasonography (EUS), ECG, SMA-12, electrolytes, CBC, and baseline carcinoembryonic antigen (CEA) level. Patients with T2-3 with any N, patients with M1a cancer, and patients with T1N1 carcinoma were considered eligible. Before registration, a multidisciplinary evaluation was carried out in every patient to ensure that cancer was technically resectable and the patient was medically operable. All patients signed a written informed consent.

Patients with T4 or T1N0 cancer were excluded. Patients with any evidence of metastatic cancer were ineligible. Patients with uncontrolled comorbid conditions were ineligible.

Treatment

The objective of the protocol was to assess the feasibility of a nonplatinum-containing chemotherapy in the three step approach using three agents before and during chemoradiotherapy. If a patient had an R0 resection, no further therapy was planned. Patients with an R1 or R2 resection or who had M1 disease were offered palliative care.

Step 1: Induction Chemotherapy

All patients had a central venous line placed. Patients received docetaxel as intravenously (IV) bolus (at 33 mg/m^2), irinotecan (at 55 mg/m^2) as IV bolus, and fluorouracil (at 2g/m^2) infusion over 24 hours once per week for 2 weeks, followed by 1 week without chemoradiotherapy. One cycle was 6 weeks long. If there was no cancer progression after the first cycle, patients received a second cycle of the induction chemotherapy. Standard premedications were used.

Step 2: Preoperative Chemoradiotherapy

Patients received up to 50.4 Gy of radiotherapy in 28 fractions. Concurrently, patients received docetaxel (20 mg/m^2) IV weekly, irinotecan (30 mg/m^2) IV weekly, and fluorouracil (300 mg/m^2 in 24 hours as continuous infusion Monday through Friday of each radiotherapy week). Standard premedications were used.

Step 3: Surgery

Five to 6 weeks after the completion of chemoradiotherapy, a complete restaging was performed and surgery was attempted. Each resected specimen was examined in an elaborate manner[28] and was reverified by one pathologist (T.T.W.), who had no knowledge of patient outcome. The pathologic response was assigned to one of two categories: pathCR or less than pathCR.

Patient Follow-Up

Each patient was assessed at 3, 6, 9, and 12 months, followed by every 6 months for an additional 2 years, and then every year or until death. Development of locoregional and/or metastatic relapse was assessed.

Tissue Specimens

All tissue specimens were obtained through an approved protocol by the University of Texas MD Anderson Cancer Care Center (Houston, TX) institutional review board. All tissue sections were matched to routine hematoxylin-eosin stained slides used to evaluate for the presence of cancer by one pathologist (T.T.W.).

Immunohistochemistry and Protein Expression

Immunohistochemic staining for activated NF-κB was performed on 4-μM formalin-fixed sections with the G96-337 monoclonal antibody (2 μg/mL) (BD PharMigen, Palo Alto, CA). This antibody recognizes p65 without cross-reacting with other Rel family members. The immunohistochemic procedure was carried out as previously described.[27] Formalin-fixed cell pellets of SKGT-4 esophageal cancer cell line (D.S. Schrump, MD, National Cancer Institute, Bethesda, MD) were placed on the same slide that the tissue and used as positive control. Only nuclear immunoreactivity was considered positive for NF-κB. The intensity of NF-κB nuclear staining was evaluated on a three-point, semi-quantitative scale as follows: (0) no staining; (1) weak to moderate staining; and (2) strong staining. The extent of cancer cells with positive NF-κB was expressed as the fraction of labeled cells (ie, staining levels 1 and 2) in the cancer fields. Cases showing labeling index of ≥5% were regarded as positive for the purpose of the analysis. This cutoff was based on the NF-κB median +2SD nuclear labeling index value of all pretreatment cancer specimens. All cancer fields present in the tissue sections were analyzed and NF-κB positivity was spatially evaluated with regard to vascular, nervous structures. The presence of cytoplasmic immunoreactivity was also recorded. Three investigators (J.I., U.M., and T.T.W.) independently determined NF-κB positivity. In the discrepant cases, a final opinion was made based on consensus by all three investigators.

Statistical Methods

Fisher's exact test and Wilcoxon rank sum test were performed to determine associations between categoric variables, such as NF-κB protein and clinical outcome.

Analyses were performed to determine overall survival (OS) and disease-free survival (DFS) time. OS was defined as the time from the registration to death. When the date of death was not available, the last follow-up date was used. Data from patients that had not died were censored. DFS was defined as the time from registration to disease recurrence or until the last follow-up date. Data from patients that were alive without disease at the time of analysis were censored. An association between NF-κB and OS or DFS was tested by comparing the Kaplan-Meier survival curves with log-rank tests used to test differences in survival distribution. After stepwise selection to determine which covariate was a significant predictor of DFS and OS, multivariate Cox proportional hazards models were fit, yielding hazard ratio estimates for NF-κB,

pathologic response, age, and postoperative N status. All statistical analysis were two sided and performed at a .05 significance level. The SAS software package 6.12 was used for computations (SAS Institute Inc, Cary, NC).

RESULTS

Patient Characteristics

Cancer tissue of 43 patients was analyzed in this study. There were 37 pretreatment cancer biopsies (pretreatment unstained tissue was unavailable in six patients), and 29 post-treatment specimens with cancer were included in the analysis. Table 1 illustrates the patient characteristics. The median age of 43 patients was 56 years (range, 35 to 72). Most patients were men (95%) and adenocarcinoma was the predominant histology. Clinical stage was as follows: stage IIA in 4.6%, IIB in 28%, and III in 67.4%.

All 43 patients underwent resection following chemoradiotherapy. PathCR was observed in 14 patients (33%), and the remaining 29 patients had a less than pathCR.

With a median follow-up time of 23 months (range, 5 to 39 months), 10 (23%) of 43 patients had locoregional or metastatic progression. The median time to locoregional and metastatic progression had not yet been reached, and the OS rate at 3 years was 67%.

Activated NF-κB Expression by Immunohistochemistry

The levels of activated NF-κB protein were immunocytochemically examined in the pretreatment cancer specimens of 37 (86%) of the 43 patients and resected in the specimens of 29 patients with chemoradiotherapy resistance (less than pathCR). Nuclear and cytoplasmic NF-κB immunoreactivity was observed in all examined specimens in both cancers and adjacent nonmalignant mucosa. Cancers expressed higher levels of cytoplasmic NF-κB compared to the adjacent nonmalignant mucosa, sometimes with a clear perimembranous reinforcement (Fig 1).

Aberrant expression of NF-κB was observed in 10 (27%) of 37 pretreatment cancer biopsies and in 20 (69%) of the 29 cases with residual cancer in the resected specimen.

Pretreatment and post-treatment cancer specimens were available from 24 patients and among these, ten specimens (42%) had NF-κB positive cancers before and after treatment; six specimens (25%) were NF-κB negative before and after treatment; one specimen (4%) was NF-κB positive only before treatment; and seven specimens (29%) became NF-κB positive after treatment.

Twenty-one (49%) of the 43 patients' cancers were NF-κB positive in at least one specimen (pre- or post-treatment). NF-κB positivity was not associated with pretreatment patient characteristics, including the location of primary and clinical staging.

Table 1. Patient Characteristics

Characteristic	No. of Patients	%
Sex		
Male	41	95
Female	2	4.7
Mean age, years	56	
SD	7.9	
Range	35-72	
Histologic type		
Adenocarcinoma	42	98
Squamous cell carcinoma	1	2
Primary sites		
Middle	2	5
Distal	31	72
GEJ	10	23
Pretreatment stage, EUS		
T stage		
T1	0	0
T2	5	12
T3	38	88
N stage		
N0	11	26
N1	32	74

Abbreviations: SD, standard deviation; GEJ, gastroesophageal junction; EUS, endoscopy-ultrasound staging.

NF-κB Activation and Pathologic Response to Preoperative Chemoradiotherapy

When considering NF-κB status either before or after treatment, only one (7%) of 14 patients achieving a pathCR had NF-κB positive cancer, but 21 (72%) of the 29 patients with less than pathCR had NF-κB positive cancer ($P = < .001$, Fisher's exact test; Table 2).

When considering NF-κB status only in the pretreatment cancer biopsies, only one (7%) of 14 patients achieving pathCR had NF-κB positive cancer compared with nine (39%) of the 23 patients achieving a less than pathCR had NF-κB positive cancer ($P = .05$, Fisher's exact test; Table 2).

Of 24 patients with less than pathCR, in whom pre- and post-treatment samples were available, nine patients had pretreatment NF-κB positive cancer (among these eight patients had persistence of NF-κB positivity after treatment). In 15 patients with pretreatment NF-κB negative cancer, nine (60%) cancers became NF-κB positive following treatment. Interestingly, five of these nine cancers presented with a diffuse and strong cytoplasmic staining in their pretreatment specimens (Fig 1, panel a).

The specimens with less residual cancer cells had significantly higher post-treatment NF-κB labeling indices compared to specimens with more cancer ($P = .005$, Wilcoxon test).

NF-κB Expression and Clinical Outcome

On univariate analysis, positive NF-κB was statistically associated with shortened DFS ($P = .0006$, log-rank test, Fig 2). At a median follow-up time of 23 months, nine (43%) of 21 patients with NF-κB positive cancer developed a relapse compared to zero of 22 patients with NF-κB negative cancer. The 2-year DFS rate for patients with NF-κB positive cancer was 39% (95% CI = 26% to 52%) compared to 74% (95% CI, 63% to 84%) for patients with NF-κB negative cancer.

Similarly, the OS of patients with NF-κB positive cancer was significantly shortened ($P = .0013$, log-rank test; Fig 3). At a median follow-up of 23 months, ten (48%) of 21 patients with NF-κB positive cancer had died from cancer compared with only one (5%) of 22 patients with NF-κB negative cancer. The 2-year OS rate for patients with NF-κB positive cancer was 31% (95% CI, 20% to 43%) compared to 71% (95% CI, 61% to 82%) for patients with NF-κB negative cancer.

When considering only pretreatment cancer biopsies, the presence of activated NF-κB had a statistically significant trend towards poor survival (Fig 4). At a median follow-up time of 23 months, the

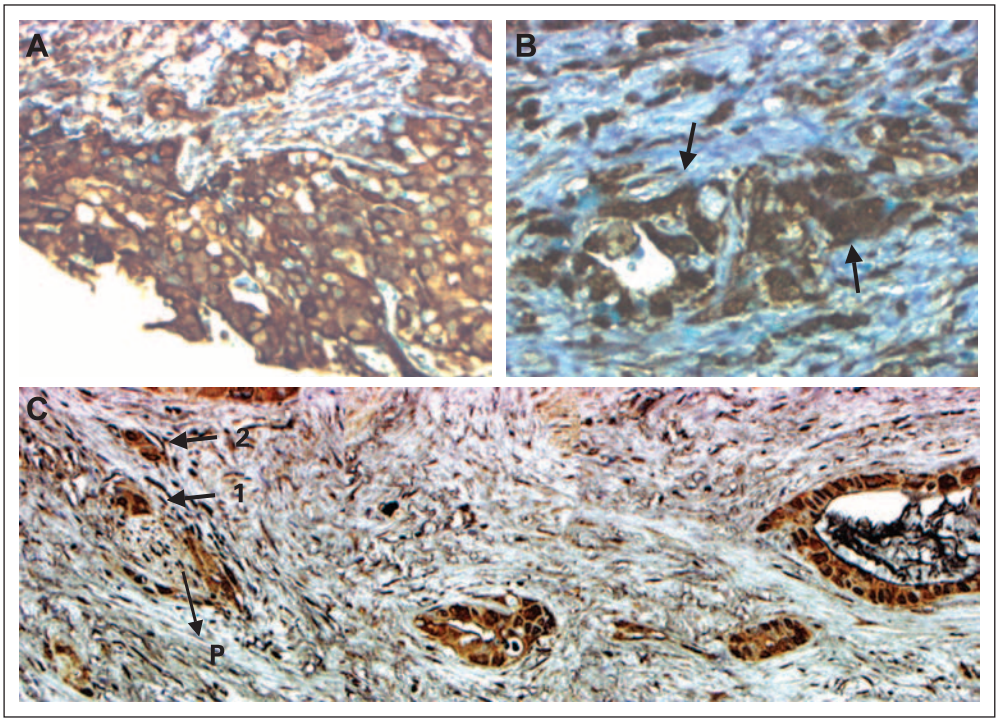


Fig 1. Immunohistochemical detection of nuclear factor κB (NF-κB) expression in esophageal cancers. (A) High levels of cytoplasmic NF-κB protein were detected in the pretreatment tumor biopsy, and strong nuclear NF-κB protein expression was detected in the residual chemo-radioresistant tumor of a esophageal cancer patient achieving less than pathologic (B; gross residual disease: > 50% residual). Arrows indicate tumor cells. (C) Indicates that the NF-κB expressing tumor cells were detected infiltrating in a perineural space (arrow 1) and connective tissue (arrow 2) in a chemo-radioresistant residual tumor (minimal residual disease: 1% to 10% residual). P, perineural space.

median survival of ten patients with NF-κB positive cancer was 13 months, but that of 27 patients with NF-κB negative cancer was not reached ($P = .06$). Additionally and intriguingly, four of five patients with worse outcome in the pretreatment NF-κB negative group developed activated NF-κB in the residual carcinoma.

In multivariate models that considered pretreatment clinical stage, lymph nodes metastases, pathCR versus less than pathCR, and age, activated NF-κB was the only significantly independent predictor of DFS ($P = .010$) and OS ($P = .015$). The hazard ratios of 0.069 for DFS and 0.079 for OS indicated that NF-κB positive cases were recurring and patients were dying at 14.5 and 12.7 times, respectively, the rate of NF-κB negative cases (Table 3).

NF-κB and Pattern of Metastasis

Pathologic cancer characteristics, such as degree of differentiation; evidence of perineural, vascular, and lymphatic invasion; and lymph node metastases in the untreated biopsy specimen, were correlated with NF-κB protein expression and patient outcome. The presence of positive NF-κB was statistically significantly associated with aggressive pathologic characteristics. Of the 21 NF-κB positive cancers, 14 (66%) demonstrated perineural, lymphatic, and/or vascular invasion compared to only two (9%) of 22 NF-κB negative cancers demonstrated aggressive features ($P = .0004$, Fisher's exact test). Figure 1 (C) shows NF-κB positive residual cancer cells penetrating a perineural space. Aggressive features were associated with poor outcome. Of 21 patients with NF-κB positive cancer, eight (38%) developed distant metastasis, and one (5%) had a regional relapse compared to none of 22 patients with NF-κB negative cancer ($P = .001$, Fisher's exact test). Of interest the only pathCR patient with positive pretreatment NF-κB developed early metastatic disease.

Table 2. NF-κB Expression and Type of Pathologic Response

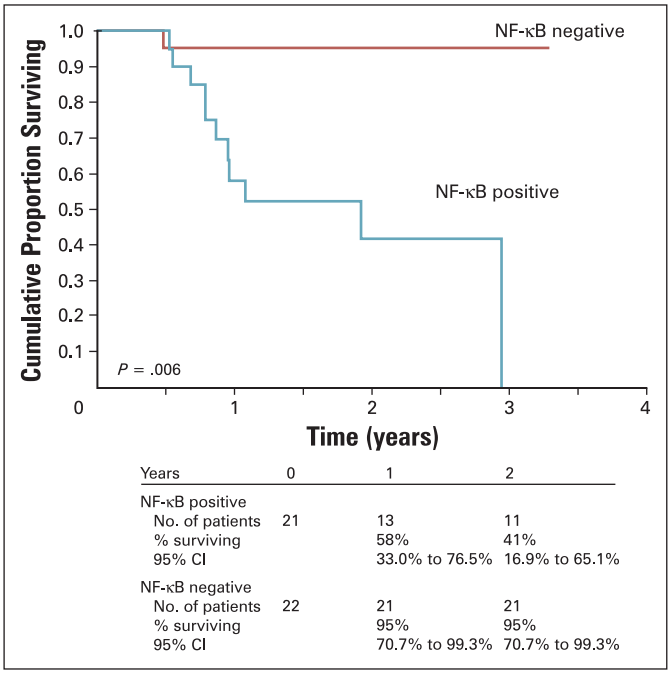
Pathologic Response	No. of Available Specimens	Positive	Negative	*P*
Pretreatment NF-κB status				< .05*
PathCR	14	1	13	
< PathCR	23	9	14	
Pre- or post-treatment NF-κB status				< .001*
PathCR	14	1	13	
< PathCR	29	21	8	

Abbreviation: NF-κB, nuclear factor κB; pathCR, complete pathologic response.
*Fisher's exact test comparing the pathCR *v* < pathCR groups.

DISCUSSION

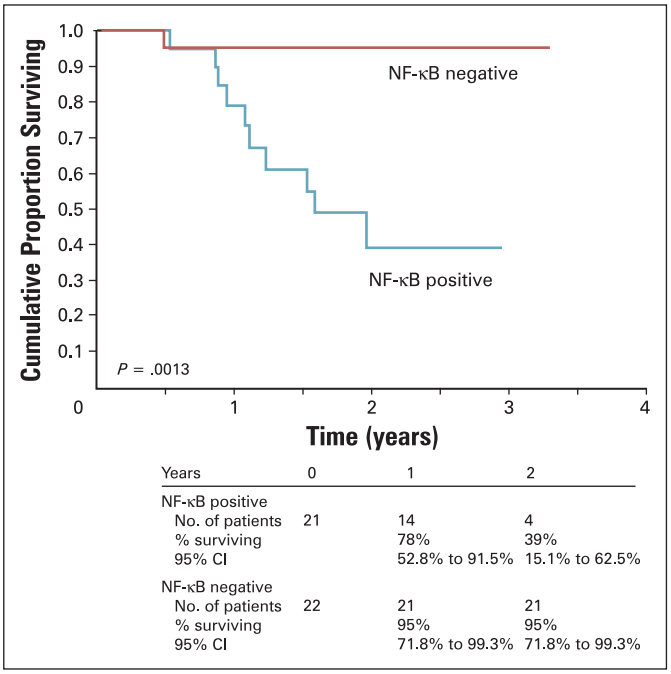
NF-κB plays a significant role in cancer progression.[17,21] NF-κB is commonly activated in esophageal carcinoma.[28,29] In the study by Abdel-Latif et al, cancer tissue samples of 97 patients with esophageal cancers were collected over a 10-year period and analyzed.[29] However, the analysis of 58 of 97 patients who received unspecified multimodality preoperative therapy might be pertinent to our study. The median survival of patients with NF-κB positive cancer was 7 months compared to 12 months for patients with NF-κB negative cancer. Even though the survival times in this study are unusually dismal for patient undergoing surgery after preoperative chemoradiotherapy, there appears to be a different clinical biology based on NF-κB expression.

Chemoradiotherapy resistance and the development of distant metastases is frequently observed in patients with localized carcinoma of the esophagus undergoing multimodality therapy. Our focus was on a group of esophageal cancer patients with



Years	0	1	2
NF-κB positive			
No. of patients	21	13	11
% surviving		58%	41%
95% CI		33.0% to 76.5%	16.9% to 65.1%
NF-κB negative			
No. of patients	22	21	21
% surviving		95%	95%
95% CI		70.7% to 99.3%	70.7% to 99.3%

Fig 2. Kaplan-Meier curve and disease-free survival by nuclear factor κB (NF-κB) expression status for esophageal cancer patients treated by preoperative chemoradiotherapy. All statistical tests were two sided. N and S indicate, respectively, the number of patients at risk and the Kaplan-Meier estimate of disease-free survival at 0, 1, and 2 years after registration. 95% CI for the Kaplan-Meier survival estimate. The numbers of subjects evaluated at 0, 1, and 2 years after registration are 21, 16, and 11 for the NF-κB positive group and 22, 21, and 21 for the NF-κB negative group, respectively.



Years	0	1	2
NF-κB positive			
No. of patients	21	14	4
% surviving		78%	39%
95% CI		52.8% to 91.5%	15.1% to 62.5%
NF-κB negative			
No. of patients	22	21	21
% surviving		95%	95%
95% CI		71.8% to 99.3%	71.8% to 99.3%

Fig 3. Kaplan-Meier curve and overall survival by nuclear factor κB (NF-κB) expression status for esophageal cancer patients treated by preoperative chemoradiotherapy. All statistical tests were two sided. N and S indicate, respectively, the number of patients at risk and the Kaplan-Meier estimate of survival at 0, 1, and 2 years after registration. 95% CI for the Kaplan-Meier survival estimate. The numbers of subjects evaluated at 0, 1, and 2 years after registration are 21, 14, and 4 for the NF-κB positive group and 22, 21, and 21 for the NF-κB negative group, respectively.

locoregional disease who were well staged, and who all received exactly the same preoperative multimodality therapy including surgery under one clinical trial. We hypothesized that activated NF-κB promotes chemoradiotherapy resistance and metastatic progression. In this study, we correlated pathologic response and clinical outcome with NF-κB expression, but we also correlated histologic features and metastatic potential with NF-κB expression.

Our results are highly intriguing. Only one of 14 patients who achieved a pathCR had NF-κB positive cancer, but 72% of patients who did not achieve a pathCR had NF-κB positive cancer ($P = < .001$). This alone suggests that inhibition of NF-κB or pathways regulated by NF-κB may be potential targets to overcome chemoradiotherapy resistance. In the pretreatment setting, the levels of activated NF-κB (percentage of positive tumors cells in the specimen) were not associated with the extent of the residual disease. Interestingly, in the residual tumor specimens, NF-κB labeling indices were significantly higher in the minimal residual setting (ie, 1% to 10% residual tumor). This suggests that the presence of even a few NF-κB positive cells is sufficient to impart resistance to chemoradiotherapy. It also underscores the possibility that activated NF-κB may be a central to phenotypic expression of aggressive cancers. This is supported by evidence that NF-κB is implicated in epithelial to mesenchymal transition.[30-32]

Activated NF-κB was also significantly associated with perineural, lymphatic, or vascular invasion ($P = .0004$). This association with more aggressive histologic features translated into metastatic potential. While none of the 22 NF-κB negative patients developed metastases, eight (38%) of 21 patients with positive NF-κB developed metastases.

OS and DFS were also related to NF-κB expression. The median survival of patients with NF-κB negative cancer has not been reached, but that of patients with NF-κB positive cancer was 22 months (Fig 2; $P = .00013$). Similarly, the DFS for patients with NF-κB positive cancers was 21.5 months, but that for patients with NF-κB negative cancers has not been reached (Fig 3; $P = .0006$). In a multivariate

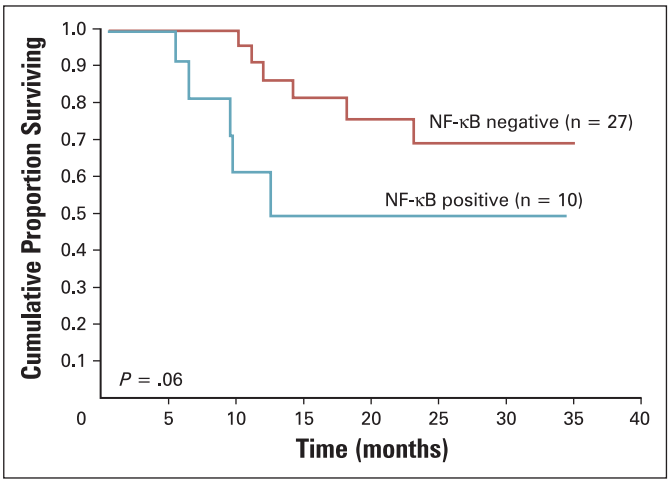


Fig 4. Kaplan-Meier curve and overall survival by pretreatment nuclear factor κB (NF-κB) expression status for esophageal cancer patients treated with preoperative chemoradiotherapy.

Table 3. Overall Survival and Disease-Free Survival for Esophageal Cancer Patients Treated With Preoperative Chemoradiation: Multivariate Analysis

Variable	Overall Survival		Disease-Free Survival	
	Hazard Ratio	P^*	Hazard Ratio	P^*
NF-κB positive	0.079	.016	0.069	.011
Clinical stage	0.823	.778	0.797	.739
pLN	2.999	.239	3.464	.199
Pathologic response	0.657	.775	0.770	.845
Age	0.984	.744	0.970	.539

Abbreviation: NF-κB, nuclear factor κB; pLN, lymph nodes positive for cancer metastases.
*χ^2 analysis comparing the variables in the multiple-regression setting.

analysis, positive NF-κB was the only independent prognostic factor for OS and DFS, yielding a considerably higher risk of recurrence and disease-related death compared to patients with NF-κB negative cancer (Table 3).

In esophageal cancer cell lines, noxious stimuli such as exposure to acid, bile, TNF-α, or cigarette smoke results in induction of NF-κB (B.B. Aggarwal, unpublished data). NF-κB can be induced following chemotherapy and radiation therapy.[33-44] However, induction of NF-κB following therapy in patients with esophageal cancer has not been described. In our study, in 15 patients with pretreatment NF-κB negative cancer, nine (60%) cancers became NF-κB positive following treatment. This suggests that activated NF-κB can be induced by chemotherapy or chemoradiotherapy in clinical situations making NF-κB a more relevant therapeutic target. Thus, understanding the underlying mechanism(s) of NFκB activation is important for the development of effective inhibitory compounds and optimal treatments.

In conclusion, our data on 43 uniformly staged and uniformly treated patients with localized esophageal cancer suggest that activated NF-κB is associated with aggressive histopathologic features, frequent metastatic potential, resistance to chemoradiotherapy, poor OS, and DFS. Understanding the biology of NF-κB mediated pathways could result in the development of effective strategies to overcome chemoradiotherapy resistance and metastatic progression.

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The authors indicated no potential conflicts of interest.

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GLOSSARY

NF-κB (nuclear factor kappa B): NF-κB is a transcriptional factor involved in the transcriptional activation of genes that regulate different cellular processes. Its nuclear location is restricted by its interaction with an inhibitor, I-κB, which sequesters it in the cytoplasm. When I-κB is phosphorylated and degraded in response to different stimuli, NF-κB becomes free to enter the nucleus.

Pathologic CR (complete response): Pathologic CR is a term used when localized carcinoma of the esophagus (but also other localized cancers) is treated (for example, with chemotherapy or chemoradiotherapy) before surgery and in the resected surgical specimen one fails to find any cancer cells (in the primary organ or accompanying lymph nodes).