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ORIGINAL ARTICLE – THORACIC ONCOLOGY

Histological Regression of Squamous Esophageal Carcinoma Assessed by Percentage of Residual Viable Cells after Neoadjuvant Chemoradiation is an Important Prognostic Factor

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ABSTRACT

Background. Whether the TNM staging system is applicable after neoadjuvant chemoradiation in esophageal cancer is controversial. The aim of this study was to evaluate the prognostic value of histopathological regression of the primary tumor in postchemoradiated patients.

Materials and Methods. The pretherapeutic and pathological ypTNM stages of patients who have had neoadjuvant chemoradiation followed by esophagectomy were analyzed. The percentage of residual viable cells of the primary tumor (ypV) and other clinicopathological factors were tested for their prognostic value.

Results. Of 175 recruited patients, 55 (31.4%) achieved pathological complete response. The median survival of these 55 patients was significantly longer than those with other disease stages (124.8 vs 21.1 months) ($P < .001$). Gender, ypT, ypN, ypTNM, and ypV stage were significant prognostic factors in univariate analysis. In patients without nodal metastases, the median survival in patients with residual viable cells in the primary tumor (ypV+) was 24.6 months, compared with that of 124.8 months in those with no viable cells (ypV0) ($P = .043$). In those who had nodal metastases, the median survival of patients with ypV0 and ypV+ were 21.2 months and 17.4 months respectively ($P = .37$). Cox regression analysis showed that male gender, high percentage of residual viable cells (ypV), and positive nodal status (ypN1) were independent predictors of poor prognosis.

Conclusions. In patients who underwent neoadjuvant chemoradiation therapy, histopathological regression of the primary tumor indicated by percentage of residual viable cells is an important prognostic factor in addition to nodal status and gender.

The American Joint Committee on Cancer (TNM) staging system is used to stratify esophageal cancer patients for different therapeutic strategies.[1] The staging system accurately predicts long-term survival in patients treated with surgical resection alone.[2] For locoregionally advanced esophageal cancer however, the outcome is generally poor after surgical resection.[3,4] In order to improve outcome, neoadjuvant chemoradiation therapy followed by surgery is increasingly used to treat esophageal cancer.[5,6] In this situation, it remains unclear if the same TNM staging system is applicable after surgery to guide prognosis. In a previous study, we have demonstrated that ypTNM staging after neoadjuvant chemoradiation was suboptimal in prognostication.[7,8] Similar findings have also been reported in the literature.[7,9,10] Evaluating histopathological regression in the surgical specimen may be a better way to assess prognosis.[11–13]

The aims of the present study were to investigate the prognostic value of the ypTNM staging system and assess the significance of the percentage of viable residual cells in the esophagus by histopathological examination in patients who had had received neoadjuvant chemoradiation therapy.

PATIENTS AND METHODS

From 1995 to 2007, 183 patients who had squamous cell esophageal carcinoma and who received neoadjuvant chemoradiation followed by surgery at the Queen Mary Hospital, The University of Hong Kong, were included in this study. Neoadjuvant chemoradiation treatment was given as part of a randomized controlled trial comparing neoadjuvant chemoradiation versus surgical resection alone or when locally advanced tumor or nonregional metastatic nodal spread was present. In these situations, a R0 resection was judged not probable and thus chemoradiation was used upfront. Patients with systemic organ metastases were not selected for surgical treatment and thus were excluded. Only patients who had R0 resections were included in this study because patients who had incomplete tumor resection invariably would have a poor prognosis. Tumors located at the cardia or nonsquamous cell cancers were excluded.

For all patients, staging investigations included upper endoscopy, endoscopic ultrasound (EUS) and bronchoscopy, ultrasound of the neck with or without fine-needle aspiration cytology of suspected nodes, computer tomography (CT), or positron emission tomography fusion with computer tomography (PET/CT) imaging (PET/CT scan was available since 2003). Chemoradiation therapy was given in a concurrent manner. The chemotherapy regime comprised cisplatin at 100 mg/m^2 on day 1 and then day 22 and continuous infusion of 5-fluorouracil (5-FU) at 500 mg/m^2 per day for 5 days from days 1 to 5 and days 22 to 26. Radiotherapy was given at a dosage of 40–46 Gy at 2 Gy per fraction. It was delivered through anterior and posterior opposing fields to the primary esophageal tumor covering at least 1-cm lateral margins and 3-cm axial margins. Postchemoradiation evaluation was performed 4 weeks after the date of finishing the treatment course, and surgery carried out soon after.

The choice of surgical approach was governed by the location of the tumor. For tumors located in the middle and lower thirds of the esophagus a Lewis-Tanner esophagectomy through an abdominal-right thoracotomy approach was preferred, but three-phase esophagectomy and minimally invasive techniques using thoracoscopic ± laparoscopic approaches have been increasingly employed in recent years. Two-field lymph node dissection was performed. Bilateral cervical nodal dissection was not routine because evidence was not strong enough to demonstrate clear benefits over two-field lymphadenectomy but with potentially increased morbidities.[14,15]

Pathological Analysis

Pathological preparation of the surgical specimen started immediately after the operation. A surgeon identified the lymph node groups in the specimen. They were dissected and labeled separately from the main esophageal specimen. Two designated pathologists (KWC, AKYL) were responsible for the histological examination. The esophagus was fixed in 10% neutral formalin overnight, serially sectioned, and embedded into paraffin blocks. Sections were cut at 5 μm thickness and stained with hematoxylin and eosin for microscopic examination. The tumor zone on the slide was labeled respectively as scar tissue, necrotic tissue, and viable tumor. Percentage of the viable residual tumor was then calculated by dividing the viable residual tumor area by the total tumor area, which is the sum of the areas categorized under the tumor zone. The percentage of viable residual tumor was designated as a continuous variable and also categorized into 4 groups as a measure of the extent of chemoradiation response: ypV0, no viable cell; ypV1, 1%–33% viable tumor; ypV2, 34%–66% viable tumor; and ypV3, 67%–100% viable tumor, according to the Guidelines of Japanese Society for Esophageal Disease.[16] The deepest layer involved by malignant cells determined the ypT-stage. The total number of harvested lymph nodes and the location and the number of lymph nodes with metastasis were recorded. A final pathologic stage (ypTNM stage) was then assigned to each specimen according to the American Joint Committee on Cancer criteria.

Statistical Analysis

All data were collected prospectively. Categorical data were analyzed using chi-square and Fisher exact tests where appropriate. Continuous variables are expressed as median (range). Survival was calculated by the Kaplan–Meier method from the date of operation to the time of death or last date of assessment. Log-rank test was used to compare survival difference between groups. Prognostic factors for survival were assessed using Cox regression for univariate analysis and Cox proportional hazards models were fitted for multivariate analysis (backward stepwise [conditional LR]). Differences between groups were considered statistically significant if the P values were less than .05. The statistical analysis was performed with SPSS Software for Windows (SPSS, Chicago, IL).

TABLE 1 Demographic features of patients treated with neoadjuvant chemoradiation and univariate analysis of survival in relation to clinicopathological characteristics

Characteristics	No. of patients ($n = 175$) (%)	HR	(95% CI)	P value
Age, median (range)	65 (38–82)	0.994	0.974–1.015	.596
Gender				.004
Male	149 (85.1)	3.1	1.422–6.761	
Female (reference)	26 (14.9)	1		
Level of tumor				.787
Cervical (reference)	2 (1)	1		
Upper	32 (18.3)	1.330	0.175–10.101	.783
Middle	104 (59.5)	1.838	0.254–13.321	.547
Lower	31 (17.7)	1.762	0.233–13.319	.583
Double	6 (3.5)	1.253	0.113–13.902	.854
Clinical stage (pretreatment)				
cT stage				.300
cT1	3 (1.7)	1		
cT2	14 (8.0)	1.556	0.285–8.503	.610
cT3	149 (85.1)	0.500	0.133–1.876	.304
cT4	9 (5.1)	1.174	0.429–3.215	.755
cN stage				.246
cN0	37 (21.1)	1		
cN1	138 (78.9)	1.352	0.812–2.252	
cM stage				.194
cM0	146 (83.4)	1		
cM1	29 (16.6)	1.432	0.833–2.460	
cTNM stage				.281
c-stage I (reference)	3 (1.7)	1		
c-stage II	33 (18.8)	0.487	0.111–2.133	.340
c-stage III	110 (62.9)	0.727	0.177–2.983	.658
c-stage IV	29 (16.6)	0.951	0.218–4.145	.947
Pathological stage				
ypT stage				.006
ypT0/pTis (reference)	78 (44.6)	1		
ypT1	17 (9.6)	1.844	0.947–3.588	.072
ypT2	36 (20.6)	1.485	0.841–2.624	.173
ypT3	39 (22.3)	2.626	1.543–4.467	<.001
ypT4	5 (2.9)	2.963	0.899–9.768	.074
ypN stage				.001
ypN0 (reference)	111 (63.4)	1		
ypN1	64 (36.6)	2.020	1.325–3.081	
ypM stage				.79
ypM0 (reference)	161 (92)	1		
ypM1	14 (8)[a]	1.119	0.488–2.566	
ypTNM				.003
ypCR (reference)	55 (31.4)	1		
ypT0N1M0	20 (11.4)	2.594	1.245–5.406	.011
y-stage I	13 (7.4)	2.579	1.188–5.601	.017
y-stage II	51 (29.2)	2.377	1.312–4.304	.004
y-stage III	22 (12.6)	4.041	2.075–7.873	<.001
y-stage IV	14 (8)[a]	2.254	0.892–5.695	.086

TABLE 1 continued

Characteristics	No. of patients ($n = 175$) (%)	HR	(95% CI)	P value
Residual tumor				
ypV stage[b]	175 (100%)	1.334	1.127–1.579	.001
ypV stage[c]				.003
ypV0 (0%) (reference)	78 (44.6)	1		
ypV1 (1–33%)	42 (24)	1.538	0.900–2.630	.116
ypV2 (34–66%)	18 (10.3)	2.065	1.013–4.209	.046
ypV3 (66–100%)	37 (21.1)	2.659	1.579–4.476	<.001

HR hazard ration, *CI* confidence interval

Reference against which hazard rations are calculated

[a] Stage IV by virtue of distant nodal metastases, distant organ metastases patients were excluded

[b] pV stage tested as a continuous variable

[c] pV stage tested as a categorical variable

RESULTS

Of the 183 patients who had chemoradiation followed by surgery, 175 had total tumor clearance (R0) achieved and were included in this study. Among these patients, 149 were men and the median age was 65 (range, 38–82). The median follow-up was 20 months (range, 1–143). The demographic data of these patients are shown in Table 1.

Effects, Morbidities, and Mortalities

A total of 132 (75.4%) patients had their tumor downstaged, the tumor status of 35 patients (20.0%) remained unchanged, and 8 patients (4.6%) had disease progression after chemoradiation. For surgery-related morbidities, 9 patients (5.1%) had anastomotic leakage and 5 patients (2.9%) had chylothorax. Major medical complications including chest infection, arrhythmia, and myocardial infarction occurred in 20 patients (11.4%). Also, 1 patient (0.6%) died in hospital. He had a prolonged stay in hospital after surgery because of socioeconomic reason. He eventually died of pneumonia with no evidence of recurrence.

Survival Analysis

At the time of data analysis, 73 patients had died; 17 of them died from non-tumor-related cause. Overall survival was investigated. The overall median survival of all patients was 39.2 months. The 3-year and 5-year survival rates were 52.8% and 40.2%, respectively. Univariate analysis showed that the pretreatment clinical stage was not a predictor of overall survival. The potential prognostic factors identified were gender, pathological T stage (ypT), pathological N stage (ypN), and the overall pathological stage (ypTNM) (Table 1). ypV stage was tested as both a continuous and categorical variable. For the latter, the ypV stage was categorized into 4 groups according to the Guidelines of Japanese Society for Esophageal Disease. In either situation, ypV stage was a significant prognostic factor in univariate analysis.

Male gender was a predictor of poor survival, and the survival curve is shown in Fig. 1a. Overall, ypTNM stage-specific survival curves are shown in Fig. 1b. No statistical difference could be identified between each stage of disease by log-rank test. The median survival of the 55 patients (31.4%) who had pathological complete response (ypT0N0M0) was significantly longer compared with those with other ypTNM stages combined, at 124.8 months vs 21.1 months, $P < .00$ (Fig. 1c).

Survival curves of different ypT stages from analysis of the primary tumor status are illustrated in Fig. 2a. Advancing ypT stages had worse prognosis. The median number of harvested lymph nodes was 22 (range, 0–97). Among the study group, 64 patients (36.6%) had positive malignant lymph nodes (ypN+). The median survival of patients with nodal metastases was 21 months compared with 65.2 months in patients without nodal metastases ($P < .001$) (Fig. 2b). Of the 111 patients (63.4%) without nodal metastasis, 56 (32%) had viable malignant cells identified in the primary tumor (ypV+). The median survival of these patients was 24.6 months, which was significantly worse when compared with the 55 patients (31.4%) who had no viable cells in the primary tumor (ypV0), whose median survival was 124.8 months ($P = .043$) (Fig. 2c). In contrast, in patients who had nodal metastases, survival of patients with ypV0 and ypV+ was not significantly different; median survival was 21.2 months and 17.4 months, respectively ($P = .368$) (Fig. 2d).

Multivariate analyses using Cox proportional hazard model for survival is shown in Table 2. ypV as a continuous variable, gender, ypT, ypN and overall ypTNM stage were entered into the model. Male gender, the percent of
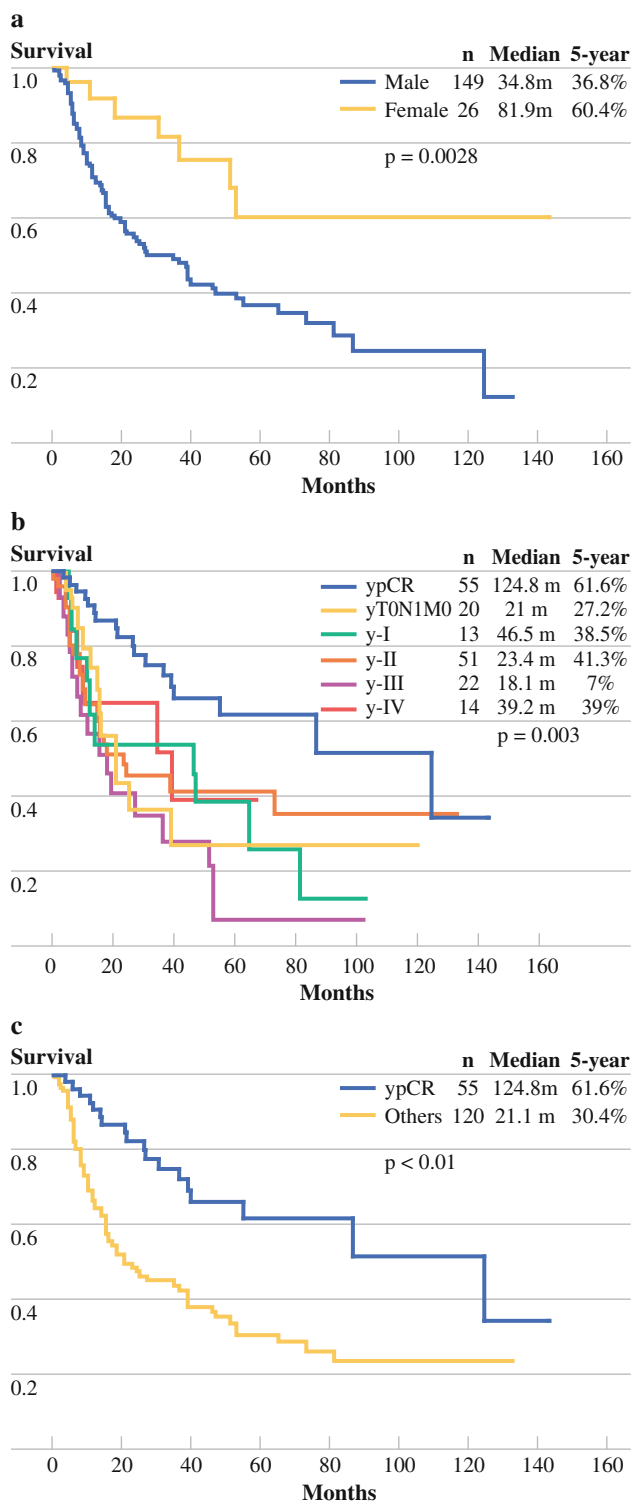
FIG. 1 **a** Survival curve with gender as a predictor of survival. **b** Survival curve of overall ypTNM stage for patients treated with neoadjuvant chemoradiation followed by surgery. **c** Survival curve for patients with pathological complete response (ypCR) and other stages (others) of disease

viable malignant cells in the primary tumor (ypV), and presence of metastatic lymph node (ypN) were independent predictors of poor prognosis. Survival of subcategories of ypV stages is shown in Fig. 2e. A trend of separation of survival is seen among different ypV stages. ypV as a categorical variable, gender, and ypN were re-entered to the Cox model for analysis. All three variables were found to be independent poor prognostic predictors (Table 3).

DISCUSSION

In this study, we have shown that in patients who underwent neoadjuvant chemoradiation therapy before surgical resection, percentage of viable cells in the primary tumor, nodal status, and gender were prognostic factors on multivariate analysis. ypV stage could potentially replace ypT stage. Nodal status is however even more important; positive nodal metastasis incurs a poor prognosis even in the presence of complete response in the primary tumor.

The beneficial effects of neoadjuvant chemoradiation therapy, although gaining popularity, have not been consistently shown in randomized trials.[3,4,17–21] However, patients who have pathological complete response (ypT0N0M0) after neoadjuvant chemoradiation therapy have repeatedly been shown to have better survival compared with those with incomplete response.[22–25] In our group of patients, chemoradiation had substantial effects; 75.4% of patients were downstaged, and 31.4% achieved complete response. Consistent with other reports, the long-term survival of the complete responders was significantly longer than those patients with residual tumor.[4,19,26] The 3-year and 5-year survival rates in ypCR patients were 72.1% and 61.6%, respectively.

Pretherapeutic clinical TNM stage had no impact on survival. This is not unexpected since long-term prognosis would depend on the response to neoadjuvant treatment. This is also consistent with the findings from other similar studies.[8,27] It is however controversial whether postsurgical ypTNM stage is of prognostic significance or not. The relevance of ypTNM has been variably reported by different investigators.[10] Swisher and associates identified ypTNM as an independent prognostic factor on multivariate analysis, while data from the Memorial Sloan Kettering Center did not find it of value.[9] Our data could not demonstrate the significance of ypTNM stage on multivariate analysis. ypT stage was not prognostic on multivariate analysis, only ypN was useful. The reason that ypTNM stage was not prognostic may be related to an altered relationship between ypT and ypN stage. In our previous study, we have shown that while in patients who had sur-

FIG. 2 a Survival curve dependent on ypT stage disease. **b** Survival curve for patients with (ypN+) or without (ypN0) nodal metastases. **c** Survival curve of ypV0 (without residual malignant cells in primary tumor) versus ypV+ (with residual malignant cells) in patients with ypN0. **d** Survival curve of ypV0 (without residual malignant cell in primary tumor) versus ypV+ (with residual malignant cell) in patients with ypN+. **e** Survival curve of patient in relation to the amount of viable cell categorized according to the Guidelines of Japanese Society for Esophageal Disease
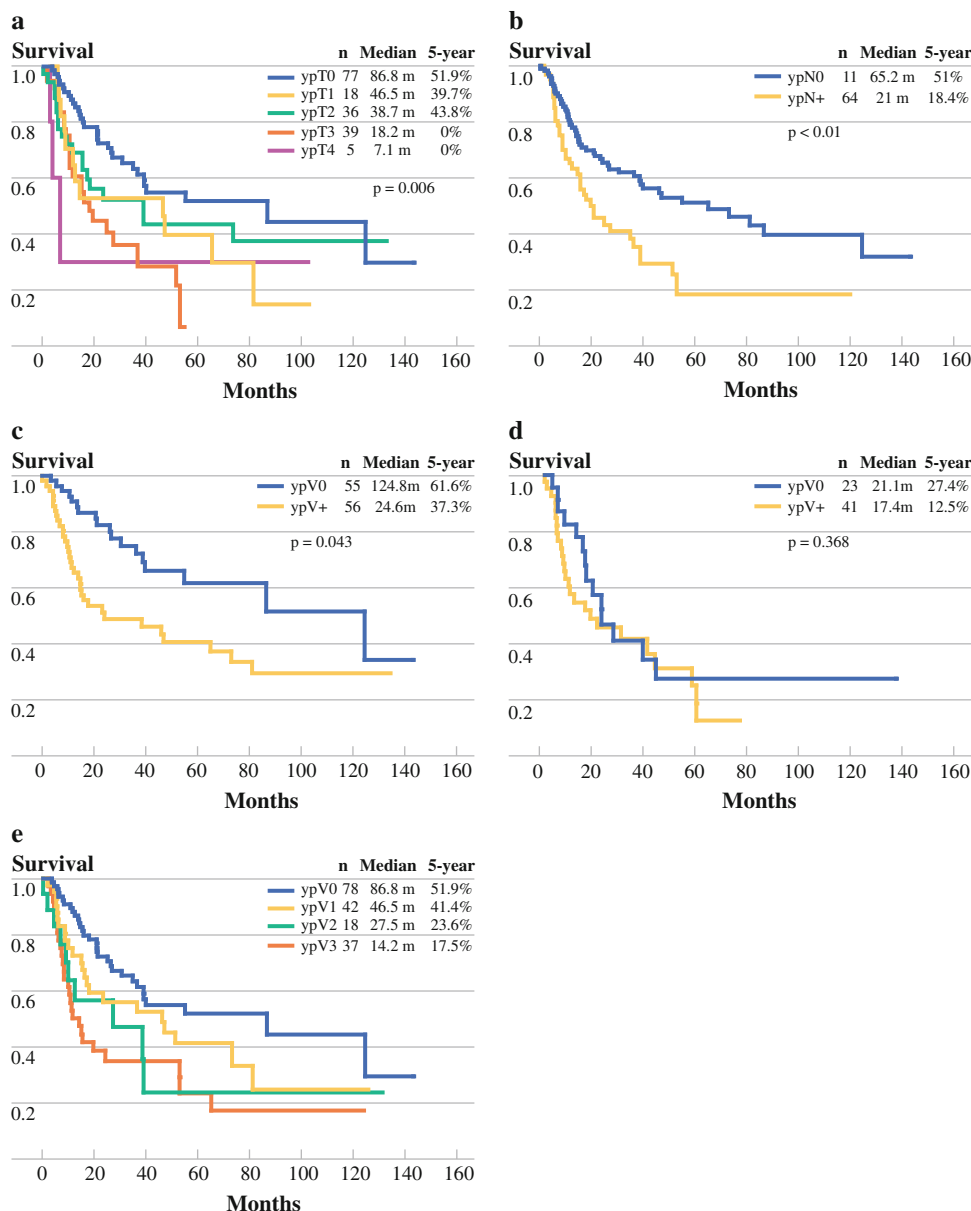

TABLE 2 Multivariate analysis on factors predictive of survival of patients treated with neoadjuvant chemoradiation and surgery

	HR	95% CI	P value
Gender			
Male	3.011	1.381–6.567	.006
Female (reference)	1		
ypN stage			
ypN0 (reference)	1		
ypN1	1.713	1.118–2.625	.013
ypV stage	1.362	1.151–1.612	<.001

HR hazard ratio, *CI* confidence interval

Reference against which hazard rations are calculated

gical resection alone without prior treatment there was a linear relationship between the chance of nodal metastasis and pT stage, this clear association was lost in those who had had chemoradiation.[7] Response in the primary tumor does not necessarily imply equal response in the lymph nodes. The metastatic cells may behave differently, or they may be located outside the irradiation field.

There are difficulties assigning ypT stage in patients who had prior treatment. The conventional TNM classification denotes a pT stage according to the deepest layer of the esophageal wall that is infiltrated by the tumor. After neoadjuvant treatment, this simple gradation is lost. Often only small clusters of residual viable cells are found in the deep layer of the esophagus, with the superficial layers

TABLE 3 Multivariate analysis on factors predictive of survival with residual viable cell as categorical variable

	HR	95% CI	P value
Gender			
Male	3.042	1.390–6.567	.005
Female (reference)	1		
ypN stage			
ypN0 (reference)	1		
ypN1	1.712	1.117–2.624	.014
ypV stage			.005
ypV0 (reference)	1		
ypV1	1.561	0.912–2.672	.105
ypV2	1.829	0.894–3.739	.098
ypV3	2.592	1.530–4.386	<.001

HR hazard ratio, *CI* confidence interval

Reference against which hazard rations are calculated

V0: No residual viable malignant cell in primary tumor. V1: 1%–33% of residual malignant cell remaining in primary tumor. V2: 34%–66% of residual malignant cell remaining in primary tumor. V3: 67%–100% of residual malignant cell remaining in primary tumor

sterilized. It is not clear if assigning a ypT stage according to this layer is appropriate. Instead, looking at the percent of residual viable tumor may be a better way to measure the severity of disease status.

Different grading systems have been reported to assess the degree of primary tumor response after neoadjuvant therapy (Table 4). Mandard and associates first reported the importance of taking into account the degree of tumor

regression as an important survival prognostic factor.[28] The grading system was based on the amount of residual viable cells and posttherapeutic fibrosis. Schneider divided the percent of viable cells into 0%, <10%, 10%–50%, and >50%.[11] Chirieac used slightly different dividing points as 0%, 1%–50%, and >50%.[8] The Japanese Society for Esophageal Disease published a guideline to assess the degree of primary tumor response by dividing the proportions of viable cell into thirds.[16] From our data, it seems certain that ypV is of prognostic significance both as a continuous or a categorical variable (Tables 2 and 3). For the ease of daily clinical application, the ability to divide ypV into discrete grades could be useful. A clear trend is seen in survival from ypV0 to ypV3 (Fig. 2e). However, the choice of different categories is arbitrary. Consistently reproducible categories are not yet available in the literature. This may in part be related to different ways of assessing histological regression. One potential limitation on assessing the percent of viable cells is that spontaneous tumor necrosis can occur in any tumor, particularly if the necrosis is confined to the center of a large tumor cell clump, and this may not be related to treatment effect. Distinction between the two mechanisms is not possible by histological examination. A scar area is presumed to have developed after tumor necrosis. However, scarring might occur without prior tumor's presence.

Undoubtedly, nodal status is an important prognostic factor. The ypN stage is shown in the present study as an important factor. Gaca et al. demonstrated in 101 patients who had chemoradiation that the ypN status was the only

TABLE 4 Currently available grading systems for evaluation of the primary tumor response after chemoradiation therapy

Authors	Tumor grading	Features of primary tumor
Chirieac LR et al. 2005[8]	1	0% of residual cell
	2	1%–50% of residual viable cell
	3	>50% of residual viable cell in primary tumor
Schneider PM et al.[11]	1	>50% vital residual tumor cells (VTRCs)
	2	10%–50% VTRCs
	3	<10% VTRCs
	4	0 VTRCs
Japanese Society of Esophageal Disease[16]	0	Ineffective
	1	Slightly effective: Viable cell more than 1/3 of tumor tissue, but with evidence of degeneration
	2	Moderately effective: Viable cell less than 1/3 of tumor tissue and severely degenerated or necrotic
	3	Markedly effective: No viable cell
Mandard AM et al. 1994[28]	1	Complete response + fibrosis
	2	Scattered viable cells + fibrosis
	3	Increased number of viable cell but fibrosis still predominated
	4	Amount of residual cells outgrowing fibrosis
	5	Absence of regressive change

prognostic factor for disease-free survival.[29] Similar findings were reported by Reynolds et al.[27] It is important to note that in our patients who had ypN0 disease, ypV0 patients survived longer than those who had ypV+ disease. This difference was not significant in patients who had nodal metastases (ypN+). This is not unexpected as the importance of metastatic disease overrides the status of the primary tumor.

In summary, we have shown that the pretherapeutic clinical TNM stage has no prognostic value in patients who had neoadjuvant chemoradiation. Gender, nodal status, and the percent of residual viable cells in the primary tumor were independent prognostic factors. ypV assessment should replace conventional ypT stage as a prognostic factor.

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