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ORIGINAL ARTICLE – THORACIC ONCOLOGY

A Multifactorial Histopathologic Score for the Prediction of Prognosis of Resected Esophageal Adenocarcinomas After Neoadjuvant Chemotherapy

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ABSTRACT

Background. For esophageal adenocarcinoma treated with neoadjuvant chemotherapy, postoperative staging classifications initially developed for non-pretreated tumors may not accurately predict prognosis. We tested whether a multifactorial TNM-based histopathologic prognostic score (PRSC), which additionally applies to tumor regression, may improve estimation of prognosis compared with the current Union for International Cancer Control/American Joint Committee on Cancer (UICC) staging system.

Patients and Methods. We evaluated esophageal adenocarcinoma specimens following cis/oxaliplatin-based therapy from two separate centers (center 1: $n = 280$; and center 2: $n = 80$). For the PRSC, each factor was assigned a value from 1 to 2 (ypT0-2 = 1 point; ypT3-4 = 2 points; ypN0 = 1 point; ypN1-3 = 2 points; ≤50 % residual tumor/tumor bed = 1 point; >50 % residual tumor/tumor bed = 2 points). The three-tiered PRSC was based on the sum value of these factors (group A: 3; group B: 4–5; group C: 6) and was correlated with patients' overall survival (OS).

Results. The PRSC groups showed significant differences with respect to OS ($p < 0.0001$; hazard ratio [HR] 2.2 [95 % CI 1.7–2.8]), which could also be demonstrated in both cohorts separately (center 1 $p < 0.0001$; HR 2.48 [95 % CI 1.8–3.3] and center 2 $p = 0.015$; HR 1.7 [95 % CI 1.1–2.6]). Moreover, the PRSC showed a more accurate prognostic discrimination than the current UICC staging system ($p < 0.0001$; HR 1.15 [95 % CI 1.1–1.2]), and assessment of two goodness-of-fit criteria (Akaike Information Criterion and Schwarz Bayesian Information Criterion) clearly supported the superiority of PRSC over the UICC staging.

Conclusion. The proposed PRSC clearly identifies three subgroups with different outcomes and may be more helpful for guiding further therapeutic decisions than the UICC staging system.

Preoperative chemo- or radiochemotherapy (CTX or RCTX) followed by resection has been shown to provide survival benefit for patients with locally advanced esophageal adenocarcinoma compared with surgery alone[1–4]. Accurate postoperative staging is important for correct estimation of prognosis and for further therapeutic decisions. The new Union for International Cancer Control/

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American Joint Committee on Cancer (UICC/AJCC) TNM classification (7th edition; TNM7) shows a better prognostic stratification for primary resected esophageal cancer compared with the 6th edition (TNM6)[5,6]. However, the accuracy of this current classification in neoadjuvant-treated esophageal adenocarcinoma is unknown[7]. For gastric cancer, we have recently demonstrated that a multifactorial histopathologic prognostic score (PRSC) that included the factors ypT category, ypN category and degree of histopathological tumor regression[8] could accurately classify three groups of patients with different outcomes after neoadjuvant CTX followed by surgery[9]. In this study we investigated whether a similar, but tumor site-specific, PRSC can be applied in esophageal adenocarcinoma. Moreover, we aimed to determine whether this PRSC may provide a more accurate estimation of the prognosis compared with the current UICC/AJCC staging system.

MATERIALS AND METHODS

Patients

Three hundred and sixty resection specimens from patients with histologically confirmed, locally advanced esophageal adenocarcinoma [staged cT3/4 N(any) cM0] from two independent academic centers were investigated. There were 14 females (3.9 %) and 346 males (96.1 %), with a median age of 57 years (range 25–80 years). The median survival, which was calculated from the day of surgery onward, was 37 months (95 % confidence interval [CI] 28–45 months). There was no difference between both centers regarding age, gender distribution, or survival. Patients had undergone neoadjuvant cis/oxaliplatin/5FU-based CTX (mainly cisplatin/5FU/leucovorin regimen) followed by esophagectomy without adjuvant treatment between 1995 and 2010 at the Department of Surgery at the Technische Universität München ($n = 280$) or the University of Heidelberg ($n = 80$)[10]. Eighteen patients in the Munich cohort and 13 patients in the Heidelberg cohort (total 31 patients) had been treated with additional radiotherapy. The protocols for neoadjuvant treatment had been approved by the Institutional Review Boards. Table 1 summarizes tumor and patient characteristics, including treatment.

TABLE 1 Tumor and patient characteristics of the two patient cohorts

Factor	Center 1 (Munich)	Center 2 (Heidelberg)	Total
ypT category			
ypT0	21	17	38
ypT1	39	4	43
ypT2	51	13	64
ypT3	165	42	207
ypT4	4	4	8
ypN category			
ypN0	121	38	159
ypN1	52	20	72
ypN2	57	7	64
ypN3	50	15	65
Distant metastases			
Absent	235	64	299
Present	45	16	61
Tumor grading			
G1	2	0	2
G2	94	29	123
G3	149	49	198
G4	10	0	10
R category			
R0	231	80	311
R1	43	0	43
R2	6	0	6
Tumor regression grade (Becker)			
TRG1a	21	17	38
TRG1b	59	8	64
TRG2	63	11	77
TRG3	137	44	181
Neoadjuvant treatment			
PLF	167	9	176
PLF-Taxol	65	1	66
OLF	22	3	25
EOX	2	48	50
RCTX	18	13	31
Other platin-based CTX	6	6	12
Total	280	80	360

PLF cisplatin/5FU/leucovorine, *OLF* oxaliplatin/5FU/leucovorin, *EOX* epirubicin, oxaliplatin, capecitabin, *RCTX* radiochemotherapy (≥45 Gy cis/oxaliplatin based)

Histopathologic Evaluation

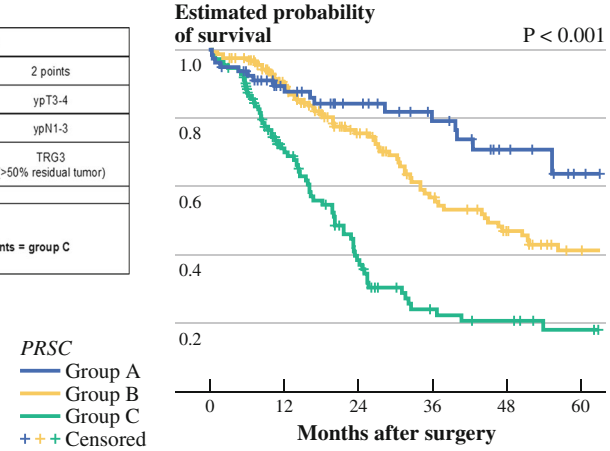
The resection specimens had been prospectively examined according to a standardized protocol[8,11] which included the investigation of the entire macroscopically identifiable tumor or the area with scarring indicating the previous site of the tumor (the tumor bed). Tumor regression grading (TRG; according to Becker et al.[8]) was based on an estimation of the percentage of residual tumor tissue in relation to the macroscopically identifiable tumor bed at the primary site of the tumor, consisting of three grades: grade 1—complete or subtotal regression (<10 % residual

FIG. 1 Histopathologic prognostic score (PRSC): **a** construction of PRSC; **b** PRSC and 5-year overall survival

a

	value	
Parameter	1 point	2 points
ypT category	ypT0-2	ypT3-4
ypN category	ypN0	ypN1-3
tumor regression grade	TRG1a; TRG1b; TRG2 (<50% residual tumor)	TRG3 (>50% residual tumor)
Prognosis score (PRSC): 3 points = group A; 4-5 points = group B; 6 points = group C		

b



tumor per tumor bed; grade 1a is complete regression and grade 1b is subtotal regression); grade 2—partial tumor regression (10–50 % residual tumor per tumor bed); and grade 3—minimal or no tumor regression (>50 % residual tumor per tumor bed). All cases were reclassified according to the current UICC/AJCC TNM system[12].

Prognostic Score

Analogous to our previous study in gastric cancer,[9] the factors TRG, ypT and ypN category were first each assigned a point value according to the respective prognostic impact (see electronic supplementary material [ESM] file 1): TRG (TRG factor): grade 1 and grade 2 (i.e. <50 % residual tumor) = 1 point; grade 3 (i.e. ≥50 % residual tumor) = 2 points; UICC/AJCC ypT category (ypT factor): ypT0–ypT2 = 1 point; ypT3–ypT4 = 2 points; UICC/AJCC ypN category (ypN factor): ypN0 = 1 point; ypN1–ypN3 = 2 points. The raw PRSC consisted of the sum of the values of these single factors with a possible range from 3 to 6 points, and was further subclassified into three groups of patients according to the survival curves of each sum score: Group A with a sum of 3 points, group B with a sum of 4–5 points, and group C with a sum of 6 points (Fig. 1; see also ESM file 2).

Statistical Analysis

IBM SPSS statistics 21 software (SPSS Inc., Chicago, IL, USA) and SAS V9.2 (The SAS Institute, Cary, NC, USA)were used for statistics. Descriptive associations between single variables were evaluated by Chi squared tests and Fisher's exact tests. Univariate analysis of survival was performed using the Kaplan–Meier method to estimate survival probabilities in patient subgroups, and the log-rank test was used for statistical comparisons. Cox proportional hazard models were performed to investigate multivariate relationships of covariates with survival. Ninety-five percent CIs were used to determine the effect of each variable on outcome. All tests were two-sided, and the significance level was set at 5 %. In order to estimate the goodness-of-fit of each PRGS model in comparison to UICC/AJCC staging, the Akaike Information Criterion (AIC) and Schwarz Bayesian Information Criterion (SBC) were used. Both methods adjust the −2 log likelihood statistics for the number of parameters in the model and number of observations used. Lower values of AIC and SBC indicate superior model fit with the 'best' model showing the lowest values for both.

TABLE 2 PRSC and UICC/AJCC stages

	UICC/AJCC stage					Total
	0[a]	I	II	III	IV	
PRSC						
A	28	47	0	0	5	80
B	0	21	69	51	26	167
C	0	0	0	83	30	113
Total	28	68	69	134	61	360

UICC/AJCC Union for International Cancer Control/American Joint Committee on Cancer, *PRSC* histopathologic prognostic score

[a] No UICC/AJCC stage for ypT0yN0

RESULTS

Pathologic Findings

The histopathologic findings of the tumors are given in Table 2. The survival curves, demonstrating the prognostic relevance of the value assignment of each single factor, are provided in the ESM supplemental file 1. No significant survival difference was found between the two patient groups of the two different surgical centers with respect to the respective factor subclassifications.

Regarding single TNM parameters and tumor regression, a significant association was noted between tumor regression and the UICC ypT and ypN categories (each $p < 0.001$) in the total patient cohort of both centers. However, of the 66 cases with a subtotal tumor regression, 20 (30.3 %) had an infiltration of the adventitial tissue and beyond, and were therefore classified as ypT3 (19 cases, Fig. 1) and ypT4 (one case). Five of the 38 patients (13.2 %) with complete regression of the primary tumor had lymph node metastases, and five (13.2 %) had distant metastases.

According to the UICC/AJCC anatomic staging system, 20 patients (5.6 %) had UICC/AJCC tumor stage IA, 48 patients (13.3 %) had stage IB, 52 patients (14.4 %) had stage IIA, 17 patients (4.7 %) had stage IIB, including three patients with complete tumor regression at the primary site of the tumor but with ypN1. Of 51 patients (14.2 %) with stage IIIA tumors, one patient had complete tumor regression at the primary site and but ypN2. Thirty-seven patients (10.3 %) were stage IIIB, 46 patients (12.8 %) were stage IIIC and 61 patients (16.9 %) had stage IV tumors, among them five patients with complete tumor regression. Twenty-eight patients (7.8 %) had no residual tumor at the primary site and no lymph node metastases. No difference was found between the two centers regarding the distribution of UICC/AJCC stages.

Prognostic Score

The PRSC classified three groups of patients: group A with 80 patients (22.2 %), group B with 167 patients (46.4 %), and group C with 113 patients (31.4 %). In the Munich cohort, group A comprised 60 patients (21.4 %), group B comprised 137 patients (48.9 %), and group C comprised 83 patients (29.6 %). In the Heidelberg cohort 20 patients (25 %) were classified into group A, and 30 patients (37.5 %) each into group B and group C. No significant difference was noted between both centers regarding the distribution of prognostic groups.

Comparison with Prognosis

The PRSC showed a highly significant association with prognosis in the whole case collection ($p < 0.0001$), Munich collective ($p < 0.0001$), and the Heidelberg collective ($p = 0.015$). Regarding the whole case collection, the PRSC discriminated significantly between the three prognostic groups. In group A, the median overall survival (OS) was not reached. Group B patients had a median OS of 45 months (95 % CI 31–58 months), and group C patients had a median OS of 20 months (95 % CI 14–26 months). The overall difference was highly significant ($p < 0.001$, log rank analysis), as were the differences between groups A and B ($p = 0.029$), groups A and C ($p < 0.001$) and groups B and C ($p < 0.001$; Fig. 1). The PRSC also showed a significant prognostic value when separately analyzing the completely resected tumors without distant metastases ($p < 0.001$), the homogenous group of patients with PLF treatment ($p < 0.001$), the heterogenous group with other platin-based treatment ($p < 0.001$), and the small group of patients who were treated with RCTX ($p = 0.023$).

In a multivariate analysis including the factors PRSC, tumor differentiation (grading), resection category, and the presence or absence of distant metastases at the time of surgery, the PRSC ($p < 0.001$; hazard ratio [HR] 1.93; 95 % CI 1.44–2.60) and tumor grading ($p = 0.006$; HR 1.54; 95 % CI 1.31–2.09) were independent prognostic factors. The PRSC was still an independent prognostic factor when analyzing both cohorts separately (data not shown).

Union for International Cancer Control/American Joint Committee on Cancer (UICC/AJCC) Staging

There was a strong association between the UICC/AJCC anatomic staging system and the PRSC ($p = 0.001$). All patients with UICC/AJCC stages III and higher were in the unfavorable PRSC group C. However, there were 16 patients in the PRSC group A who had a UICC/AJCC II stage, and nine patients who would be classified as UICC III or IV. On the other hand, 21 patients in the PRSC group B were classified as UICC/AJCC stage I, and 77 patients were classified into the prognostically unfavorable UICC/AJCC stages III/IV (Table 2). UICC/AJCC staging was prognostically relevant for stages 0, I, II, III, and IV ($p < 0.001$; see Fig. 2a) and also when probing for the anatomic substages 0, IA, IB, IIA, IIB, IIIA, IIIB, IIIC, and IV (see Fig. 2b). However, patients with anatomic stage IA had an outcome similar to those with stage IIa, whereas stage IB patients had the best clinical outcome, which was even better than patients with complete tumor regression and without lymph node metastases (ypT0N0). A multivariate analysis including the factors UICC/AJCC staging, tumor regression, resection category, and tumor grading (differentiation) showed tumor regression ($p = 0.005$; HR 1.34; 95 % CI 1.09–1.65), tumor grading ($p = 0.003$; HR 1.66; 95 % CI 1.18–2.33), and resection status ($p = 0.017$; HR 1.58; 95 % CI 1.09–2.3) as independent prognostic factors, in contrast to UICC/AJCC staging ($p = 0.058$; HR 1.08; 95 % CI 0.99–1.17).

Moreover, the comparison between the PRSC and the UICC staging groups showed significant advantages for the PRSC with higher hazard ratios and lower AIC and SBC

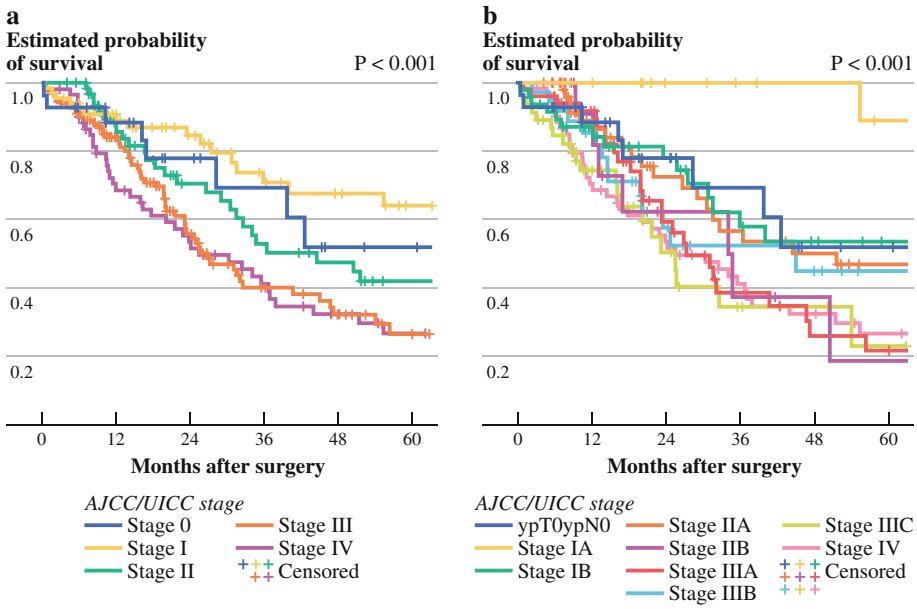


FIG. 2 UICC/AJCC anatomic staging: **a** UICC/AJCC anatomic staging and 5-year overall survival; **b** UICC/AJCC anatomic staging with subgroups and 5-year overall survival. *UICC/AJCC* Union for International Cancer Control/ American Joint Committee on Cancer

TABLE 3 Comparison of various goodness-of-fit criteria and tests of significance

	PRSC	UICC (with subgroups)	UICC (0, I, II, III, IV)
Total collective			
p Value	<0.0001	<0.0001	0.0065
HR (95 % CI)	2.2 (1.7–2.8)	1.15 (1.1–1.2)	1.1 08 (1.0–1.1)
AIC	1530.757	1553.758	1566.636
SBC	1533.787	1556.789	1569.667
Munich			
p Value	<0.0001	<0.0001	0.0015
HR (95 % CI)	2.48 (1.8–3.3)	1.2 (1.1–1.3)	1.1 (1.0–1.2)
AIC	1108.319	1123.707	1137.93
SBC	1111.081	1126.469	1140.692
Heidelberg			
p Value	0.0154	0.5997	0.9291
HR (95 % CI)	1.7 (1.1–2.6)	1.03 (0.9–1.2)	1.0 (0.9–1.1)
AIC	260.691	266.61	266.881
SBC	262.275	268.194	268.464

PRSC histopathologic prognostic score, *UICC* Union for International Cancer Control, *HR* hazard ratio, *AIC* Akaike Information Criterion, *SBC* Schwarz Bayesian Information Criterion

values compared with the UICC staging groups. This was also found when analyzing the subcohorts of the collective and when comparing the UICC stages grouped to stages I, II, III, and IV without subgroups (Table 3). Therefore, the PRSC can be regarded as a more desirable model for prognostication in this patient collection.

DISCUSSION

We demonstrated in two cohorts of neoadjuvantly-treated patients with esophageal adenocarcinoma that an easily applicable scoring system (PRSC), which includes the factors UICC/AJCC ypT category, ypN category, and the degree of histopathological tumor regression serves as a simple but highly useful post-treatment and postoperative classification system. The PRSC revealed an accurate correlation with survival, thereby discriminating three groups of patients with significantly different outcomes. The proposed PRSC also had better performance regarding the estimation of prognosis than the current UICC/AJCC staging system in our collective.

The prognosis of patients with locally advanced esophageal adenocarcinoma has improved over the last decades due to advances in surgical techniques, patient selection, and staging methods,[13,14] and due to the now widely performed multimodal treatment with peri- or preoperative CTX or chemoradiotherapy[1–4,15]. Complete or subtotal tumor regression can be observed in up to 30 % of patients after CTX, a finding that has a significant prognostic impact. Another 20 % of patients show partial tumor regression after neoadjuvant treatment[1,3,11]. The impact of histopathologic tumor regression after neoadjuvant treatment may even exceed the prognostic impact of the depth of tumor invasion (i.e. ypT category)[11,16,17]. Classification of tumor regression grade (TRG), which represents one part of the PRSC, has been proven to be objective and reproducible[18,19]. We used the TRG system according to Becker, which is based on the estimation of the percentage

of residual tumor[8,11,18,20]. Other authors use similar percentage-based steps of residual tumor to define different TRGs, and have also described the 50 % cutoff for residual tumor as prognostically relevant[21,22]. These systems, as well as the Mandard classification,[23] which is based on the estimation of the relation of fibrosis to vital tumor, could be easily applied for the proposed PRSC since the relevant categories can be used in parallel to our system. The second important parameter, which heavily influences patient's outcome, is the presence of lymph node metastases[11,22,24]. Although tumor differentiation was also an independent prognostic factor in our study, and is also implemented by the AJCC into the prognostic staging of early stages of untreated tumors,[25,26] we did not include this factor in our PRSC. There may be considerable differences between the determination of tumor grading in preoperative biopsies and the corresponding resection specimen[27]. Furthermore, in the context of a multimodal setting, it has to be emphasized that the estimation of tumor differentiation in CTX- or RCTX-treated tumors in post-treatment specimens may not be representative of the tumor due to the marked therapy-induced cytotoxic changes (e.g. regression, cytopathic effects and high-grade cellular atypia[8,28]). Moreover, in single cases, preoperative biopsy material may be scarce and only contain superficial, highly altered cellular material that may be sufficient for a malignant diagnosis but not for accurate estimation of tumor differentiation. The recently updated UICC/AJCC TNM system (TNM7)[12] recognizes esophageal adenocarcinoma as a separate tumor entity in contrast to esophageal squamous cell carcinoma. Several changes, compared with the previous UICC/AJCC TNM classification (TNM6),[29] resulted in additional prognostic information[5,26,30–32]. Although advantages of the updated UICC/AJCC TNM system could also be demonstrated for patients undergoing neoadjuvant treatment,[24,33] staging systems that have been originally developed for untreated, primary resected tumors may have limitations because they do not consider regressive alterations of the tumors[16]. Regarding the previous TNM6 UICC/AJCC staging system, several publications have addressed this issue and have proposed alternatives or modifications to the UICC/AJCC staging system[16,22,34]. In our collectives, there were marked limitations, particularly in the lower UICC/AJCC stages, regarding the prognostic value of the proposed staging categories. Stage IA patients had the best outcome, whereas stages II–IV showed similar overall survival curves. Moreover, no explicit staging is provided for tumors that show a complete regression of the primary site of the tumor and absence of lymph node metastases. These ypT0ypN0 tumors had a slightly worse outcome compared with stage IA tumors. By contrast, classification of tumors that show complete regression of the primary tumor but not of lymph node or distant metastases, which was observed in ten cases, should result in a classification of stage IIB or higher. Unfortunately, the number of cases with this finding was too low to achieve reliable knowledge concerning the biological significance of vital metastases in cases with complete tumor regression of the primary tumor site. However, our results clearly show the limitations of the UICC/AJCC staging system to accurately discriminate prognostically relevant groups in our large cohort of esophageal adenocarcinoma patients.

CONCLUSIONS

The easily applicable PRSC revealed an accurate correlation with survival and outperformed the current UICC staging system. Because a similar score is also applicable in gastric cancer,[9] such prognostically relevant, post-treatment and postoperative classification systems may be considered for future clinical practice in tailoring the treatment of patients with locally advanced adenocarcinomas of the upper gastrointestinal tract after neoadjuvant treatment.

DISCLOSURE The authors declare no conflicts of interest.

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