PART I

Staging and prognostication

CHAPTER 3

Prospective impact of tumor grade assessment in biopsies on tumor stage and prognostic grouping in gastroesophageal adenocarcinoma: relevance of the 7th edition AJCC staging manual revision

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ABSTRACT

BACKGROUND

In the 7th edition of the AJCC staging system for esophageal cancer, tumor grade was introduced as an independent determinant of stage grouping in early stage tumors. With the significantly lower prognosis of poorly differentiated early stage adenocarcinomas, these tumors might become candidate for neoadjuvant therapy, given an accurate identification of these tumors with preoperative staging. The purpose of this study is to investigate the accuracy of preoperative histopathologic grading and the effect of preoperative grade on tumor stage/prognostic grouping.

PATIENTS AND METHODS

Preoperative tumor grade was compared to postoperative tumor grade in 427 patients who were treated with surgery without neoadjuvant therapy for adenocarcinoma of the esophagus. The impact of preoperative tumor grade on stage/prognostic grouping was investigated.

RESULTS

The overall accuracy of preoperative tumor grade assessment was 76% when unknown differentiation was regarded as well/moderately differentiated as recommended by AJCC, while accuracy was 73% after exclusion of tumors with unknown grade. In patients with T1-2N0 stage tumors, 16% were assigned to a lower stage group based on preoperative pathology, whereas 5% were assigned to higher stage group. In the T1-2N0 group, sensitivity for detecting a poorly differentiated tumor was 0.43 (0.30-0.56), whereas specificity was 0.94 (0.90-0.98).

CONCLUSIONS

With increasing use of neoadjuvant therapy, accuracy of preoperative biopsy assessment has become increasingly important. In the current study, we demonstrate that accuracy of preoperative tumor grade is 73%, leading to changes in AJCC stage/prognostic group in 21% of patients with T1-2N0 esophageal adenocarcinomas. Caution should therefore be exhibited in staging patients with esophageal adenocarcinoma based on preoperative biopsy data.

INTRODUCTION

The seventh edition of the American Joint Committee on Cancer (AJCC) Staging Manual has introduced several major modifications in the staging of gastric and esophageal cancer as compared to its sixth edition.[1-3] Most importantly, all tumors involving the gastroesophageal junction (GEJ) are now classified as esophageal cancers. The only exception is for GEJ tumors with the epicenter >5 cm distal to the GEJ which are coded as gastric cancer. A second important change is the incorporation of histological grade in the stage/prognostic grouping for both adenocarcinoma and squamous cell carcinoma esophageal cancer. For T1-2N0M0 adenocarcinomas, the degree of differentiation is now an independent determinant of stage/prognostic group. Well and moderately differentiated T1N0 adenocarcinomas are staged IA, whereas poorly differentiated T1N0 adenocarcinomas are grouped together with well to moderately differentiated T2N0 tumors in stage IB. Poorly differentiated T2N0 adenocarcinomas are stage IIA. For T3 or higher stage tumors and tumors with positive lymph nodes, the degree of differentiation does not influence stage/prognostic grouping. A third change is the definition of nodal (N) status, which is now based on the absolute number of positive lymph nodes and is synchronized to nodal stage for gastric carcinoma. Additional changes include the definition of tumor stage of Tis (in situ carcinoma), T4, and M classification.

The proposal of the 2010 AJCC staging system for esophageal cancer is based on a combined large international database: the Worldwide Esophageal Cancer Collaboration (WECC).[4] This database contains information of more than 7,000 patients and represents the practice of 13 institutions on 3 continents. However, for the staging system, only data from the 4,627 patients who received surgery without chemotherapy or radiotherapy were used. Therefore, the compliance of the staging system with patients who received preoperative or postoperative treatment is debatable.[5] Another issue with this dataset is the lack of information from preoperative biopsies. The introduction of tumor grade in the staging system is entirely based upon postoperative pathologic evaluation. However, this information is unavailable when a patient is staged prior to surgery to determine the use of neoadjuvant therapy.

Since the use of preoperative chemotherapy and radiation has become increasingly established in the treatment of resectable esophageal and GEJ adenocarcinoma,[6,7] accurate preoperative staging has become an issue of increasing clinical relevance, which is not only limited to locally advanced tumors. In the AJCC 7th ed., poor differentiation/tumor grade is used as an independent predictor of poor survival in early stage tumors. Stage-specific 10-year survival rates are 66%, 51% and 38% for stage IA (T1N0G1,2), IB (T1N0G3/T2N0G1,2), and IIA (T2N0G3), respectively.[8] Provided with these data, the group of patients with T2N0G3 tumors might become candidates for preoperative therapy, given that these tumors can be correctly identified preoperatively.

The purpose of this study was to investigate the accuracy of preoperative assessment of tumor grade of esophageal and GEJ adenocarcinoma by comparing preoperative grading

on biopsies to the postoperative surgical pathology in individuals who did not undergo neoadjuvant therapy. The second purpose was to investigate the impact of preoperative grade on tumor stage/prognostic grouping as detailed in the 7th edition of the AJCC staging manual.

METHODS

PATIENT SELECTION

Patients were identified from two prospectively maintained databases of gastric and esophageal cancer. Between January 1996 and November 2009, 1,440 patients with adenocarcinoma of the distal esophagus or GEJ without metastatic disease underwent potentially curative surgery at Memorial Sloan-Kettering Cancer Center (MSKCC). January 1996 is the time point at which an institutional electronic medical record system was introduced and is, therefore, a date from which additional information to the prospective database can be obtained. Patients who received preoperative chemotherapy or radiation were excluded, leaving 475 patients who did not receive neoadjuvant treatment. Since tumor grade was not assessed in patients with T0 and Tis disease (high grade glandular dysplasia), these patients (N = 48) were also excluded. Overall 427 patients with both preoperative biopsy and postoperative resection material were available for analysis. Patient and pathologic tumor characteristics, treatment, and follow-up data were prospectively recorded. The study was approved by the Institutional Review Board of MSKCC.

PREOPERATIVE STAGING AND HISTOLOGY

Preoperative staging was performed with varying combinations of chest radiograph, computed tomography (CT), positron emission tomography (PET) scan, endoscopic ultrasound (EUS) with biopsies, and diagnostic laparoscopy with biopsies. To avoid influence by imaging modalities on the accuracy of preoperative tumor grade analysis, each patient was assigned a preoperative stage based on the tumor grade assessed from preoperative biopsies, combined with postoperative T-, N- and M-stage. All patients underwent preoperative histopathologic evaluation by an in-house pathologist, either by evaluation of the submitted slides from referring hospitals, or by review of endoscopic biopsy specimens obtained at MSKCC. Whenever possible, all the material from patients who had multiple biopsies was reviewed.

Tumor grade was defined as well, moderately or poorly differentiated and reflected a recording of the poorest grade within the biopsy. In the final analysis, well and moderately differentiated tumors were grouped as one entity. When tumor grade was not mentioned in the pathology report, it was recorded as 'unknown'. In the time period 1996-2003, pathologists of any subspecialty participated in the assessment of these tumors but since 2004, only specialized gastrointestinal pathologists evaluated the esophageal and GEJ tumors.

SURGERY

All patients underwent a potentially curative resection of the esophagus, the GEJ, the stomach or a combination with different types of approaches depending on the tumor location and the preference of the surgeon. Surgical techniques included three-phase esophagectomy (cervico-thoraco-abdominal), Ivor-Lewis esophagectomy (right thoraco-abdominal), (left) thoraco-abdominal esophagectomy, transhiatal (cervico-abdominal) esophagectomy proximal gastrectomy and total gastrectomy.

POSTOPERATIVE HISTOLOGY AND STAGING

Staging was performed according to the new American Joint Committee on Cancer Staging guidelines (7th edition, 2010).[1] Depth of tumor invasion, number of positive lymph nodes, margin status, and the grade of differentiation were prospectively recorded, and used to calculate postoperative AJCC 7th edition T-stage, N-status and stage/prognostic group. According to the AJCC stage-grouping recommendation, tumors with unknown grades were regarded as well/moderately differentiated tumors.

Tumor grade was recorded as well, well to moderately, moderately, moderately to poorly, or poorly differentiated. These were translated to a trichotomous system of well, moderately, and poorly differentiated tumors, recording the poorest grade mentioned. In the final analysis, well and moderately differentiated tumors were grouped into one entity. Adenocarcinomas of the GEJ were classified according to a modification of the Siewert criteria, with type I tumors defined as an adenocarcinoma of the distal esophagus which may extend below the esophagogastric junction by less than 25% of the tumor mass, type II tumors defined as a carcinoma that straddles the esophagogastric junction, and type III tumors as a subcardial gastric carcinoma that involves the GEJ and may extend above the GEJ by less than 25% of the tumor mass.[9]

STATISTICAL ANALYSIS

Accuracy of preoperative staging was calculated by determining the concordance between preoperative and postoperative pathologic grade assessed from biopsies and surgical specimens, respectively. The postoperative pathologic grade was utilized as the gold standard reference point. Accuracy was expressed as the percentage of patients with the correct grade assigned. Although this yields a number that is easy to understand, it fails to reflect on the distribution of patients over different categories. Therefore, Cohen's weighted Kappa test for agreement was used as an additional measurement of accuracy of preoperative tumor grade. In general, values of Kappa from 0.20 to 0.39 are considered fair agreement, 0.40 to 0.59 are considered moderate, 0.60 to 0.79 substantial, and 0.80 outstanding.[10] Differences between groups were calculated by using Pearson's chi-square test. Survival estimates were calculated using the Kaplan Meier method, while differences between survival estimates were analyzed with the Log-Rank test. All statistical analyses were performed with SPSS Statistics 17.0.

Table 1. Patient characteristics, surgical treatment, and pathology data

	N	%
Total	427	*100.0*
Sex		
male	331	*77.5*
female	96	*22.5*
Age		
mean (SD)	66.2	(10.5)
Year of surgery		
1996-1999	147	*34.4*
2000-2004	162	*37.9*
2005-2009	118	*27.6*
Surgery		
three-phase esophagectomy	24	*5.6*
Ivor-Lewis esophagectomy	201	*47.1*
thoraco-abdominal esophagectomy	33	*7.7*
transhiatal esophagectomy	77	*18.0*
proximal gastrectomy	13	*3.0*
total gastrectomy	22	*5.2*
transabdominal	15	*3.5*
esophago/total	4	*0.9*
esophago/proximal	38	*8.9*
Siewert type		
I	125	*29.3*
II	193	*45.2*
III	109	*25.5*
Postoperative stage group		
IA	123	*28.8*
IB	60	*14.1*
IIA	14	*3.3*
IIB	75	*17.6*
IIIA	57	*13.3*
IIIB	41	*9.6*
IIIC	57	*13.3*

RESULTS

Demographic, pathologic and surgical data are summarized in Table 1. Seventy-eight percent of the patients were male and the mean age was 66.2 years. The average number of patients per year who underwent surgery without preoperative therapy decreased over time: 37 patients per year in 1996-1999, 32 patients per year in 2000-2004, and 24 patients per year in 2005-2009. Adenocarcinomas were classified as Siewert I, II or III in 30%, 46% and 24%, respectively. Survival for postoperative T1-2N0 well/moderately/unknown adenocarcinomas was significantly longer as compared to poorly differentiated tumors of the same T1-2N0 stage (Figure 1, 80% versus 56%, $P = 0.005$). Patients with preoperative stage IA, who were upstaged IB on postoperative pathology had a significantly worse prognosis as compared to those who remained stage IA on postoperative pathologic staging ($P = 0.014$, Figure 2), while there was no significant difference in overall survival with patients who were assigned stage IB preoperatively and postoperatively ($P = 0.454$). This analysis could not be performed for patients incorrectly staged between stage IB to IIA, because the number of events in this group was too few.

Figure 1. Kaplan Meier curves for T1-2N0 tumors, separated by postoperative tumor grade (N = 197)

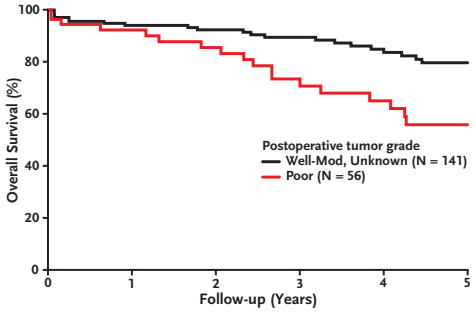
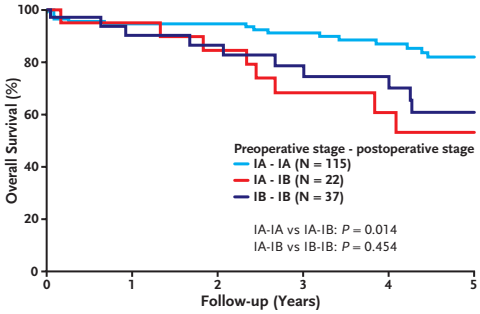


Figure 2. Kaplan Meier curves for T1-2N0 tumors, separated by preoperative and postoperative tumor stage (N = 174)



Postoperative pathology indicated 9% (37/427) of the tumors were well differentiated, 43% (183/427) moderately differentiated and 47% (199/427) poorly differentiated. Postoperative grade was reported in 98% (419/427) of the tumors, and preoperative grade was reported in 71% (302/427) of all tumors (Table 2). Based upon the AJCC staging guidelines, unknown tumor grade was recorded as well/moderately differentiated.

Accuracy of preoperative tumor grade assessment in the entire group (T1-4N0-3 patients) was 76% (324/427, $P < 0.001$) (Table 3). Cohen's kappa test for agreement demonstrated a kappa of 0.50 ($P < 0.001$), which is considered to reflect moderate agreement. Most discordance in preoperative grading in biopsies was a result of under-grading, with 29% (88/301) of all preoperative well and moderately differentiated tumors being poorly differentiated tumors on postoperative surgical pathology (Table 3). After exclusion of the patients with unknown preoperative or postoperative grade, accuracy of preoperative grading was 73% (238/301, $P < 0.001$), with a kappa of 0.58 ($P < 0.001$), indicative of moderate agreement.

The concordance of preoperative grade assessment was comparable when analyzed by specialized gastrointestinal (GI) pathologists (80%) or non-GI-pathologists (78%, P = NS). Differences in accuracy between the different Siewert groups (Siewert I: 72%, Siewert II: 79%, Siewert III: 86%) were borderline significant ($P = 0.06$).

Accuracy slightly increased during the consecutive time periods: accuracy was 73%, 81% and 83% for the periods 1996-1999, 2000-2004, and 2005-2009. This observation did not reach statistical significance.

Since tumor grade only affects stage grouping in T1-2N0 patients, subgroup analyses were performed excluding T3 and T4 tumors and tumors with positive lymph nodes. Accuracy of preoperative grade assessment in T1-2N0 tumors was 79% (156/197, $P < 0.001$), with a kappa of 0.42 (Table 4). Most grading discordance was due to preoperative under-grading. After conversion of T1-2N0 tumors into their corresponding pre and postoperative stage/prognostic groups, 79% (156/197, $P < 0.001$) of the patients were

Table 2. All $T_{1-4}N_{0-3}$ tumors (N = 427)

		Postoperative grade				
		Well	Moderate	Poor	Unknown	Total
Preoperative grade	Well	5	14	6	0	25
	Moderate	7	101	42	1	151
	Poor	1	14	111	0	126
	Unknown	24	54	40	7	125
	Total	37	183	199	8	427

Table 3. All $T_{1-4}N_{0-3}$ tumors (N = 427), unknown grade is coded as well/moderately differentiated
Accuracy: 324/427 = 0.76, Cohen's Kappa: 0.50

		Postoperative grade		
		Well-Mod, Unknown	Poor	Total
Preoperative grade	Well-Mod, Unknown	213	88	301
	Poor	15	111	126
	Total	228	199	427

Table 4. All $T_{1-2}N_0$ tumors (N = 197)
Accuracy: 156/197 = 0.79, Cohen's Kappa: 0.42

		Postoperative grade		
		Well-Mod, Unknown	Poor	Total
Preoperative grade	Well-Mod, Unknown	132	32	164
	Poor	9	24	33
	Total	141	56	197

Table 5. Stage grouping for all $T_{1-2}N_0$ tumors (N = 197)
Accuracy: 156/197 = 0.79, Cohen's Kappa: 0.57

		Postoperative stage group			
		IA	IB	IIA	Total
Preoperative stage group	IA	115	22	0	137
	IB	8	37	10	55
	IIA	0	1	4	5
	Total	123	60	14	197

properly staged (Table 5), with a kappa of 0.57 ($P < 0.001$). Preoperative under-staging occurred in 16% (32/197) of these patients and over-staging in 5% (9/197), respectively. Sensitivity in this group to detect a poorly differentiated tumor was 0.43 (0.30-0.56), whereas specificity was 0.94 (0.90-0.98). This indicates that of all poorly differentiated tumors in the T1-2N0 group, 57% were not identified as such.

DISCUSSION

Although T-stage, N-stage and M-stage are strong independent predictors of survival in esophageal cancer,[11-13] the sixth edition of the AJCC staging system for esophageal cancer has been challenged for its heterogeneity of outcome on survival within the different stage groups.[14] During the past years, several pathologic prognostic factors have been proposed for incorporation into the TNM staging system. These include degree of differentiation,[15] vascular and perineural invasion,[16] extracapsular lymph node invasion,[17] tumor length,[18,19] clearance of the proximal and distal resection margin,[20,21] and status of the circumferential margin.[22] These proposals however, are primarily based on analyses from relatively small series of patients, and in most instances from single institution databases. Incorporation of a new factor into the AJCC staging system not only requires a structured mechanism of the proposed change,[23] but the factor also has to be available in the collaborative WECC database.

In 1991, Robey-Cafferty et al showed in their series of 69 patients with squamous cell carcinoma of the esophagus that the degree of tumor differentiation was an independent prognostic factor.[24] In 2001, Dickson et al. proposed incorporation of tumor grade in the staging system based upon a series of 139 consecutive patients who received surgery for GEJ carcinoma (mostly adenocarcinoma). The authors demonstrated differences in 3-year overall survival for well (33.3%) and moderately differentiated tumors (28.9%) vs poorly differentiated tumors (15.9%) respectively.[15] Khan et al confirmed these results in a series of 219 patients with N0 squamous cell carcinoma and adenocarcinoma of the esophagus, showing that tumor grade was an independent prognostic factor in univariate and multivariate analysis.[25] Other studies also confirmed a correlation between tumor grade and prognosis in univariate analysis, but not in multivariate analysis.[26-28] Recently, Thompson et al reported in a study of 240 patients with mainly adenocarcinoma, that tumor grade was an independent prognostic variable in both univariate and multivariate analysis.[14] In this study, patients were divided into two groups: well and moderately differentiated, and poorly and undifferentiated. Furthermore, the combined data in WECC database also supports the incorporation of tumor grade into the 2010 AJCC staging system for esophageal cancer. The inclusion of postoperatively determined tumor grade into the staging system may provide outcome information and guidance for adjuvant therapeutic strategies. However, the question raised with this addition is how reliable is the assessment of tumor grade in small preoperative biopsies? This is particularly relevant when neoadjuvant options are considered with poorly differentiated adenocarcinomas of T2N0M0 stage.

In the patient group evaluated, the average number of patients without preoperative treatment decreased over the years. This is consistent with increased use of neoadjuvant therapy in locally advanced GEJ carcinoma. Poorly differentiated (G3) and early stage tumors were associated with a significantly lower survival rate as compared to tumors that were graded as well (G1), moderately (G2) or unknown on postoperative pathology

Figure 3. Adenocarcinoma of mixed type with moderately differentiated (lower left) and poorly differentiated component (upper)

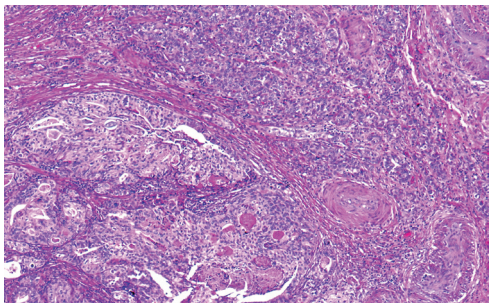
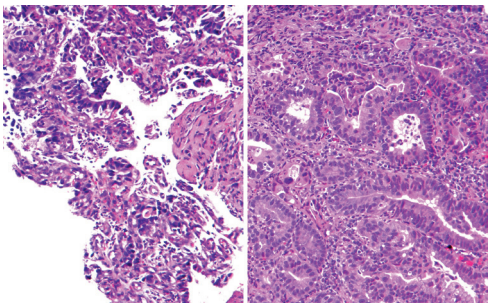


Figure 4. Preoperative biopsy (left) and corresponding surgical resection specimen (right) of a moderately differentiated adenocarcinoma



Biopsy could be upgraded as a poorly differentiated carcinoma due to its proximity to ulcer and the crush artifact

(Figure 1). Preoperatively understaged IB tumors (into preoperative stage IA) were associated with lower survival as compared to correctly staged IA tumors (Figure 2), indicating the significance of accurate tumor grade assessment on preoperative staging. In the entire cohort of this study, including patients with 'unknown' tumor grade, which was regarded as well/moderately differentiated according to AJCC recommendation, preoperative tumor grade assessed in biopsies was concordant with that assessed in surgical specimens in 76% of the patients. After excluding individuals with unknown tumor grade, overall concordance was 73% (kappa value: 0.58) consistent with moderate agreement.

However, not all stage/prognostic groups are affected by tumor grade. In the AJCC 7th Edition only stage T1-2N0 tumors are assigned to three separate stage groups when the tumor is well and moderately or poorly differentiated. In T1-2N0 tumors, the concordance for tumor grade was slightly higher as compared to the entire cohort (79% vs. 76%), and therefore 21% of this group was assigned an "inappropriate" stage group based on preoperative biopsies: under-staging occurred in 16%, and over-staging in 5%.

The differences in concordance of tumor grade assessed by GI-pathologists and non GI-pathologists were not statistically significant. To the authors' best knowledge, this has not been described previously. Siewert type showed borderline significant differences favoring higher accuracy of tumor grade assessment in Siewert III tumors.

A number of factors could account for the discordance in assessment of tumor grade in biopsy and in surgical resection specimens. These include sampling issue, technical quality of the specimen, and, to a lesser extent, the experience of the pathologist. It is of note that a significant number of GEJ adenocarcinomas reveal intratumoral heterogeneity (Figure 3), exhibiting mixed populations of well to moderately and poorly differentiated histopathology within the same tumor. Thus a biopsy specimen may not always represent the dominant component of the tumor grade in the entire lesion. Therefore, sampling bias may be responsible for discordance in both up-grade and

down-grade between biopsy and resection specimens, respectively. A second significant factor responsible for tumor grading discordance is the suboptimal preparation of biopsy specimens, which may include excessive air dry effect before formalin fixation, tumor tissue adjacent to ulcer and necrosis, or thermal/mechanically generated crush artifacts in diminutive specimens. In these situations, an up-grading from a well/moderately to a poorly differentiated tumor is a more likely consequence than down-grading from a poorly differentiated to a well/moderately tumor (Figure 4).

The very recent introduction of the 2010 staging system into clinical practice has precluded the development of treatment algorithms for the different stage/prognostic groups and these remain to be established. No prospective studies have been performed in the subset of early stage poorly differentiated tumors, and most current clinical trials of neoadjuvant therapy for esophageal adenocarcinoma apply different inclusion criteria and usually include patients with cT2-3N0[29] and cT1-3N1 tumors[7]. However, the FFCD 9901 trial showed that preoperative CRT followed by surgery has a negative impact on postoperative mortality in early stage esophageal cancer patients as compared to surgery alone, without a significant difference in overall survival.[30] The majority of patients in this trial however, had squamous cell carcinoma, while no subgroup analyses were performed on poorly differentiated early stage tumors. Furthermore, a WECC database analysis showed that the subgroup of patients with T2N0G3 tumors, when treated with surgery only, has a significantly worse 10-year survival (38%) as compared to other early stage but lower grade tumors (66% and 51%).[8]

Since the new AJCC staging system has revealed a prognostic difference for patients with IA, IB and IIA esophageal adenocarcinoma that is stratified with the combination of tumor stage (T1-2) and tumor differentiation, it is likely that patients with early esophageal and GEJ tumors, which are poorly differentiated, may become candidates for neoadjuvant therapy. However, in our study, we have demonstrated that the sensitivity for grading poorly differentiated early stage tumors correctly is only 0.43. Given this low sensitivity there exists the potential risk that more than half of these patients would not receive therapy that might be otherwise recommended.

With the increasing use of neoadjuvant chemotherapy and radiotherapy in esophageal cancers, it is evident that therapeutic management strategy should be evaluated based on a combination of clinical, radiographic, and pathologic assessments. In future modifications of the AJCC staging system, this might be addressed by capturing clinical staging information in the WECC database. Precise pathological identification is particularly pertinent when assessing tumor differentiation in individuals with early stage and lymph node negative esophageal cancer.

REFERENCES

1 Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A. AJCC Cancer Staging Manual. 7th ed. New York: Springer; 2010.

2 Rice TW, Blackstone EH, Rusch VW. *A cancer staging primer: esophagus and esophagogastric junction*. J Thorac Cardiovasc Surg 2010;139:527-529.

3 Greene FL, Page DL, Fleming ID, et al. AJCC Cancer Staging Manual. 6th ed. New York: Springer; 2002.

4 Rusch VW, Rice TW, Crowley J, Blackstone EH, Rami-Porta R, Goldstraw P. *The seventh edition of the American Joint Committee on Cancer/ International Union Against Cancer Staging Manuals: the new era of data-driven revisions*. J Thorac Cardiovasc Surg 2010;139:819-821.

5 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.

6 Cunningham D, Allum WH, Stenning SP, et al. *Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer*. N Engl J Med 2006;355:11-20.

7 Tepper J, Krasna MJ, Niedzwiecki D, et al. *Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781*. J Clin Oncol 2008;26:1086-1092.

8 Rice TW, Rusch VW, Ishwaran H, Blackstone EH. *Cancer of the esophagus and esophagogastric junction: data-driven staging for the seventh edition of the American Joint Committee on Cancer/International Union Against Cancer Cancer Staging Manuals*. Cancer 2010;116:3763-3773.

9 Siewert JR, Stein HJ. *Classification of adenocarcinoma of the oesophagogastric junction*. Br J Surg 1998;85:1457-1459.

10 Landis JR, Koch GG. *The measurement of observer agreement for categorical data*. Biometrics 1977;33:159-174.

11 Korst RJ, Rusch VW, Venkatraman E, et al. *Proposed revision of the staging classification for esophageal cancer*. J Thorac Cardiovasc Surg 1998;115:660-669; discussion 669-670.

12 de Manzoni G, Pedrazzani C, Pasini F, et al. *Pattern of recurrence after surgery in adenocarcinoma of the gastro-oesophageal junction*. Eur J Surg Oncol 2003;29:506-510.

13 Mariette C, Balon JM, Piessen G, Fabre S, Van Seuningen I, Triboulet JP. *Pattern of recurrence following complete resection of esophageal carcinoma and factors predictive of recurrent disease*. Cancer 2003;97:1616-1623.

14 Thompson SK, Ruszkiewicz AR, Jamieson GG, et al. *Improving the accuracy of TNM staging in esophageal cancer: a pathological review of resected specimens*. Ann Surg Oncol 2008;15:3447-3458.

15 Dickson GH, Singh KK, Escofet X, Kelley K. *Validation of a modified GTNM classification in peri-junctional oesophago-gastric carcinoma and its use as a prognostic indicator*. Eur J Surg Oncol 2001;27:641-644.

16 Torres CM, Wang HH, Turner JR, et al. *Pathologic prognostic factors in esophageal squamous cell carcinoma: a follow-up study of 74 patients with or without preoperative chemoradiation therapy*. Mod Pathol 1999;12:961-968.

17 D'Journo XB, Avaro JP, Michelet P, et al. *Extracapsular lymph node involvement is a negative prognostic factor after neoadjuvant chemoradiotherapy in locally advanced esophageal cancer*. J Thorac Oncol 2009;4:534-539.

18 Bollschweiler E, Baldus SE, Schroder W, Schneider PM, Holscher AH. *Staging of esophageal carcinoma: length of tumor and number of involved regional lymph nodes. Are these independent prognostic factors?* J Surg Oncol 2006;94:355-363.

19 Eloubeidi MA, Desmond R, Arguedas MR, Reed CE, Wilcox CM. *Prognostic factors for the survival of patients with esophageal carcinoma in the U.S.: the importance of tumor length and lymph node status*. Cancer 2002;95:1434-1443.

20 Dexter SP, Sue-Ling H, McMahon MJ, Quirke P, Mapstone N, Martin IG. *Circumferential resection margin involvement: an independent predictor of survival following surgery for oesophageal cancer*. Gut 2001;48:667-670.

21 Barbour AP, Rizk NP, Gonen M, et al. *Adenocarcinoma of the gastroesophageal junction: influence of esophageal resection margin and operative approach on outcome*. Ann Surg 2007;246:1-8.

22 Sillah K, Pritchard SA, Watkins GR, et al. *The degree of circumferential tumour involvement as a prognostic factor in oesophageal cancer*. Eur J Cardiothorac Surg 2009;36:368-373.

23 Gospodarowicz MK, Miller D, Groome PA, Greene FL, Logan PA, Sobin LH. *The process for continuous improvement of the TNM classification*. Cancer 2004;100:1-5.

24 Robey-Cafferty SS, el-Naggar AK, Sahin AA, Bruner JM, Ro JY, Cleary KR. *Prognostic factors in esophageal squamous carcinoma. A study of histologic features, blood group expression, and DNA ploidy*. Am J Clin Pathol 1991;95:844-849.

25 Khan OA, Alexiou C, Soomro I, Duffy JP, Morgan WE, Beggs FD. *Pathological determinants of survival in node-negative oesophageal cancer*. Br J Surg 2004;91:1586-1591.

26 Langley SM, Alexiou C, Bailey DH, Weeden DF. *The influence of perioperative blood transfusion on survival after esophageal resection for carcinoma*. Ann Thorac Surg 2002;73:1704-1709.

27 Paraf F, Flejou JF, Pignon JP, Fekete F, Potet F. *Surgical pathology of adenocarcinoma arising in Barrett's esophagus. Analysis of 67 cases*. Am J Surg Pathol 1995;19:183-191.

28 Wayman J, Bennett MK, Raimes SA, Griffin SM. *The pattern of recurrence of adenocarcinoma of the oesophago-gastric junction*. Br J Cancer 2002;86:1223-1229.

29 van Heijl M, van Lanschot JJ, Koppert LB, et al. *Neoadjuvant chemoradiation followed by surgery versus surgery alone for patients with adenocarcinoma or squamous cell carcinoma of the esophagus (CROSS)*. BMC Surg 2008;8:21.

30 Mariette C, Seitz JF, Maillard E, et al. Surgery alone versus chemoradiotherapy followed by surgery for localized esophageal cancer: Analysis of a randomized controlled phase III trial FFCD 9901. In: ASCO Annual Meeting; 2010; 2010.