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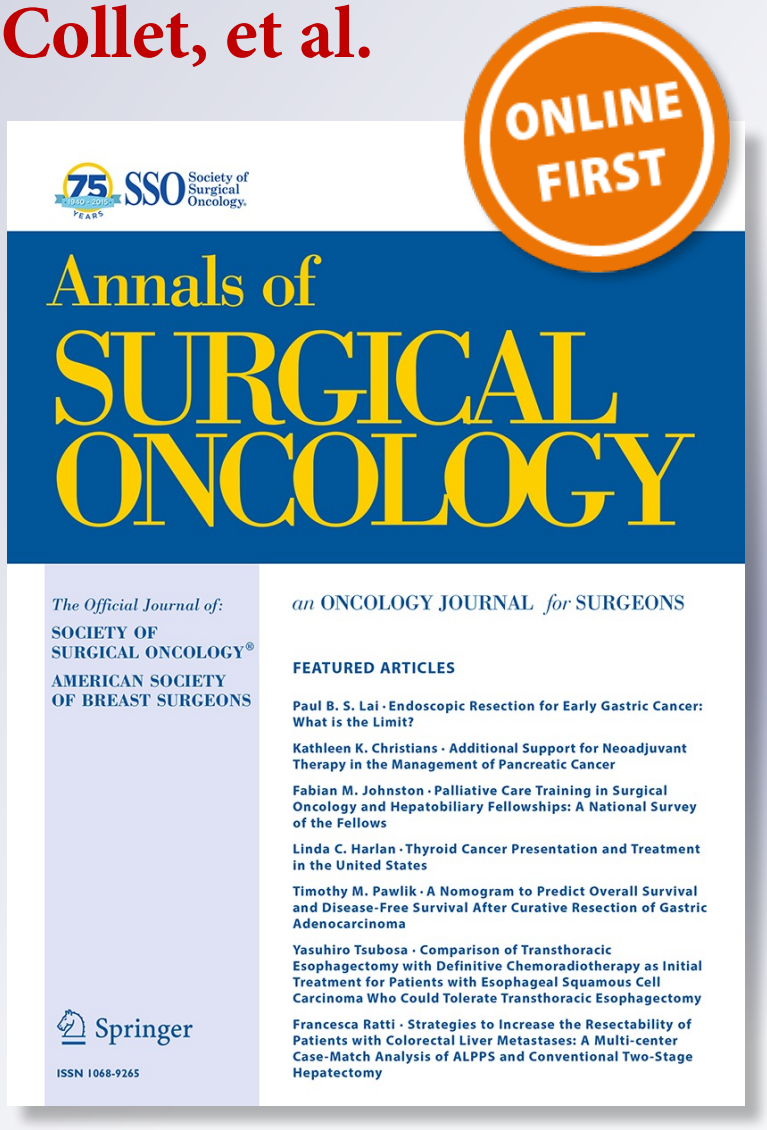


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# Predictive Factors of Recurrence in Patients with Pathological Complete Response After Esophagectomy Following Neoadjuvant Chemoradiotherapy for Esophageal Cancer: A Multicenter Study

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## ABSTRACT

**Background.** Minimal data have previously emerged from studies regarding the factors associated with recurrence in patients with ypT0N0M0 status. The purpose of the study was to predict survival and recurrence in patients with pathological complete response (pCR) following chemoradiotherapy (CRT) and surgery for esophageal cancer (EC).

**Methods.** Among 2944 consecutive patients with EC operations in 30 centers between 2000 and 2010, patients treated with neoadjuvant CRT followed by surgery who achieved pCR ($n = 191$) were analyzed. The factors associated with survival and recurrence were analyzed using a Cox proportional hazard regression analysis.

**Results.** Among 593 patients who underwent neoadjuvant CRT followed by esophagectomy, pCR was observed in 191 patients (32.2 %). Recurrence occurred in 56 (29.3 %) patients. The median time to recurrence was 12 months. The factors associated with recurrence were postoperative complications grade 3–4 [odds ratio (OR): 2.100; 95 % confidence interval (CI) 1.008–4.366; $p = 0.048$) and adenocarcinoma histologic subtype (OR 2.008; 95 % CI 0.1.06–0.3.80; $p = 0.032$). The median overall survival was 63 months (95 % CI 39.3–87.1), and the median disease-free survival was 48 months (95 % CI 18.3–77.4). Age (>65 years) [hazard ratio (HR): 2.166; 95 % CI 1.170–4.010; $p = 0.014$), postoperative complications grades 3–4 [HR 2.099; 95 % CI 1.137–3.878; $p = 0.018$], and radiation dose (<40 Gy) (HR 0.361; 95 % CI 0.159–0.820; $p = 0.015$) were identified as factors associated with survival.

**Conclusions.** An intensive follow-up may be beneficial for patients with EC who achieve pCR and who develop major postoperative complications or the adenocarcinoma histologic subtype.

**Keywords** Esophageal cancer · Chemoradiotherapy · Pathological complete response · Survival · Recurrence

Carcinomas of the esophagus and esophagogastric junction (EGJ) are the most rapidly increasing tumor types in Western countries, with 480,000 new cases diagnosed annually and 400,000 mortalities per year.[1,2] These carcinomas represent an aggressive disease, and <30 % of patients have a potentially resectable tumor at the time of

On behalf of the FREGAT (French Eso-Gastric Tumors) working group—FRENCH (Fédération de Recherche EN CHirurgie)—AFC (Association Française de Chirurgie). The members of the FREGAT (French Eso-Gastric Tumors) working group, FRENCH (Fédération de Recherche EN CHirurgie) and AFC (Association Française de Chirurgie) are given in Appendix.



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diagnosis. The majority of patients already exhibit a locally advanced tumor with the involvement of locoregional lymph nodes upon presentation.[1] For patients undergoing multimodal treatment combining neoadjuvant chemoradiotherapy (CRT) or chemotherapy (CT) with subsequent surgery, the 3-year survival rates range between 22 and 55 %.[3–6]

In patients with locally advanced carcinoma of the esophagus, neoadjuvant CRT has been proven to improve long-term survival; therefore, this treatment is recommended, especially for patients with squamous cell carcinoma (SCC).[6,7] Neoadjuvant CRT yields a pathological complete response (pCR) in 18–40 % of cases, which is a major predictive factor of survival [8–10] However, patients with pCR can exhibit tumor recurrence that is either local or metastatic. In a multicenter study focused on 299 patients with pCR, the recurrence rate was 23.4 %, and the overall and disease-specific 5-year survival rates were 55 and 68 %, respectively.[11] None of the clinicopathologic factors studied was significantly correlated with recurrence.[11] In a retrospective study, van Hagen et al. described the pattern and timing of disease recurrence in patients with pCR after neoadjuvant CRT followed by surgery for esophageal cancer.[9] Among the 188 patients included in this study, 33 % exhibited a pCR. The overall 5-year survival rate in those patients was 52 %, and the disease-specific 5-year rate was 70 %. Recurrence occurred in 24 (39 %) of 62 patients with pCR. In this study, the median time to and pattern of recurrence (locoregional and/or distant metastases) were similar for patients with and without pCR.

The present study was designed to evaluate the predictive factors of survival and recurrence in ypT0N0M0 patients treated with neoadjuvant CRT and esophagectomy for carcinoma of the esophagus.

## PATIENTS AND METHODS

### *Patients*

Data from 2944 patients who underwent surgery for carcinoma of the esophagus or gastroesophageal junction, including Siewert I and II tumors with curative intent, at 30 French-speaking European centers between 2000 and 2010 were collected retrospectively through a dedicated website (http://www.chirurgie-viscerale.org). Data collected included demographic, perioperative, and surgical characteristics. The patients selected met the following inclusion criteria: SCCs or adenocarcinomas (ADs), neoadjuvant CRT, and ypT0N0M0 status at the time of the resection. The exclusion criteria were as follows: no neoadjuvant treatment and patients receiving definitive CRT or CT. Patients were excluded if the surgical and/or tumor data required for the analysis were missing. The study was accepted by the regional institutional review board on July 15, 2013, and the database was registered on the Clinicaltrials.gov website under the identifier NCT 01927016.

### *Neoadjuvant Therapy*

The decision to treat patients with combined-modality therapy and the neoadjuvant regimen administered was determined by a multidisciplinary team and in accordance with French national guidelines (www.tncd.org). Pretherapeutic investigations included systematically a physical examination, standard laboratory screening, a digestive endoscopy with biopsies, an esophageal endoscopic ultrasound (EUS), and a thoracoabdominal computed tomography (CT) scan; 18F-fluorodeoxyglucose positron emission tomography and CT (18F-FDG PET/CT) were performed on request. Pretherapeutic cTNM classification was based on endoscopic ultrasonography and/or a CT scan in cases where tumor stenosis precluded a full endoscopic ultrasonographic examination.

Patients treated with neoadjuvant therapy usually received 5-fluorouracil and platinum salt administration for 2 to 4 cycles with concomitant 45 Gy of radiotherapy. Surgical resection was performed approximately 6 to 8 weeks after the completion of neoadjuvant therapy.

### *Surgical Resection*

All operations were performed with curative intent using one of the following methods: Ivor-Lewis (laparotomy and right thoracotomy, chest anastomosis), transhiatal (laparotomy and left neck incision, neck anastomosis), or 3-hole (laparotomy, right thoracotomy and left neck incision, neck anastomosis). The choice of operation was based on the site of the primary tumor and on the general status of the patients. Postoperative complications were graded in accordance with the Dindo–Clavien classification system.[12]

### *Histopathological Analysis*

Histological staging of tumors was based on the seventh edition of the International Union Against Cancer TNM classification.[13] pCR was defined as the absence of histological evidence of neoplasia, gross tumor, or individual cells in the entire resected esophageal specimen by light microscopy.

### *Follow-up*

The survival status of patients was determined in May 2012 and the median follow-up was 35 (range 0.1–139) months. One patient was lost to follow-up. All other

patients were followed up at the outpatient clinic 1 month after discharge and then every 6 months during the 5 years after surgery and every 12 months thereafter. A physical examination, nutritional assessment, and computed tomography were used to assess recurrence. Additionally, endoscopic examination was performed 2 years following esophagectomy. In cases with a normal workup, the patients were classified as disease-free.

### *Statistical Analysis*

Quantitative variables are expressed as the median [range], and qualitative variables are expressed as a percentage. Continuous data were compared using the Mann–Whitney *U* test, and ordinal data were compared using the $\chi^2$ or Fisher's exact test as appropriate. Overall and disease-free survivals (including postoperative deaths) were estimated using the Kaplan–Meier method. Predictive factors of survival and recurrence were analyzed using a Cox proportional hazard regression analysis, using a stepwise procedure; the 0.2 level was the cutoff for entry into the model. Additionally, clinically relevant variables were systematically included in the model. Multivariable $\chi^2$ and $p$ values were used to characterize the independence of these factors; the hazard ratio (HR) and the 95 % confidence interval (CI) were used to quantify the relationship between survival and each independent factor. The threshold for statistical significance was set at $p < 0.05$. Analyses were performed using SPSS® version 19.0 software (Statistical Package for the Social Sciences, Chicago, IL).

## RESULTS

### *Patient Characteristics*

Among 593 patients who underwent neoadjuvant CRT followed by esophagectomy, pCR was observed in 191 patients (32.2 %). The median age was 58 years [range, 30–82], and the male to female sex ratio was 5.3:1. SCC was present in 141 (73.8 %) patients. The most common neoadjuvant protocol consisted of a 5-FU-based chemotherapy regimen with a median of 2 cycles [range 2–12] and a median radiation dose of 45 Gy [range 32–68]. Adjuvant treatment was performed in 5 (2.6 %) patients (radiotherapy $n = 1$, chemotherapy $n = 4$). Patient characteristics are summarized in Table 1.

### *Surgical Characteristics*

The median number of analyzed lymph nodes in the surgical specimen was 13 [range, 1–42]. The surgical characteristics of the study population are summarized in Table 1. The Ivor-Lewis procedure was performed in 147 (77.0 %) patients. Among the 191 patients, 110 (57.6 %) patients developed postoperative complications. In particular, postoperative complications at grade 1 or 2 occurred in 50 (26.2 %) patients and at grade 3 or 4 occurred in 42 (22.0 %) patients. Postoperative 90-day mortality occurred in 18 (9.4 %) patients. The median length of stay was 19 [range, 8–130] days.

### *Recurrence*

Recurrence occurred in 56 (29.3 %) patients with a median time of 12 [range, 2–180] months. The patterns of recurrence are displayed in Table 2. The independent factors significantly associated with recurrence identified in the multivariable Cox regression analysis were postoperative complications (grade 3–4) [odds ratio (OR): 2.100; 95 % CI 1.008–4.366; $p = 0.048$) and AD histologic subtype (OR 2.008; 95 % CI 0.1.06–0.3.80; $p = 0.032$). Pretherapeutic stage (cT and cN) and radiotherapy dose were not independent factors of recurrence (Table 3).

### *Survival*

The median overall survival of the patients with pCR was 63 months [CI 95 % 39.3–87.1], and the median disease-free survival was 48 months [CI 95 % 18.3–77.4]. On multivariable analysis, age (>65 years) (HR 2.166; 95 % CI 1.170–4.010; $p = 0.014$) and postoperative complications (grades 3–4) (HR 2.099; 95 % CI 1.137–3.878; $p = 0.018$) were associated with worse survival. Moreover, radiotherapy dose <40 Gy (HR 0.361; 95 % CI 0.159–0.820; $p = 0.015$) was identified as an independent factor significantly associated with better survival (Table 4).

## DISCUSSION

pCR was observed after neoadjuvant CRT in one-third of the patients in this multicenter European study. Among these, one-third exhibited recurrence. The median time to recurrence was 12 months, and major postoperative complications and AD histologic subtype were independent factors of relapse. The median OS was 63 months, and median DFS was 48 months. Age, major postoperative complications, and radiotherapy dose were independent factors of survival in patients with pCR status.

Previous studies have established that pCR after neoadjuvant treatment is correlated with better oncologic outcomes in gastroesophageal cancer,[8–11,14–19] The 5-year OS and disease-specific survival in patients who achieved pCR were estimated to range from 52 to 79 % and 68 to

**TABLE 1** Patient characteristics of the 191 patients with ypT0N0M0 status at the time of resection

| Characteristics | Patients, $n = 191$ |
|---|---|
| Age (yr), *n* (%) | |
| <65 | 139 (72.7) |
| >65 | 52 (27.3) |
| Gender, *n* (%) | |
| Male | 161 (84.3) |
| Female | 30 (15.7) |
| ASA score, *n* (%) | |
| 1–2 | 156 (81.7) |
| 3 | 35 (18.3) |
| Malnutrition, *n* (%) | |
| Yes | 52 (27.2) |
| No | 101 (52.9) |
| Unknown | 38 (19.9) |
| Radiotherapy, median, [range], Grays | 45 [32–68] |
| Chemotherapy, median, [range], cycles | 2 [2–12] |
| Histology, *n* (%) | |
| Adenocarcinoma | 50 (26.2) |
| SCC | 141 (73.8) |
| cT, n (%) | |
| 1 | 16 (8.4) |
| 2 | 38 (19.9) |
| 3 | 114 (59.7) |
| 4 | 23 (12) |
| cN, n (%) | |
| 0 | 56 (29.3) |
| 1 | 135 (70.7) |
| Location of the primary tumor, *n* (%) | |
| Upper | 39 (20.4) |
| Middle | 72 (37.7) |
| Lower | 80 (41.8) |
| Procedure with thoracotomy, *n* (%) | |
| Yes | 180 (94.2) |
| No | 11 (5.6) |
| Anastomotic location, *n* (%)* | |
| Cervical | 38 (19.9) |
| Thoracic | 152 (79.6) |
| Surgical procedure | |
| TT 2 fields | 147 (77.0) |
| TT 3 fields | 28 (14.7) |
| Transhiatal | 9 (4.7) |
| Others | 7 (3.7) |
| Reoperation, *n* (%) | |
| No | 170 (89.0) |
| Yes | 21 (11.0) |
| Blood loss, median, [range], ml | 300 [0–2700] |
| Blood transfusion, *n* (%) | |
| No | 141 (73.8) |
| Yes | 28 (14.7) |
| Unknown | 22 (11.5) |

*ASA* score American Society of Anesthesiology score, *SCC* squamous cell carcinoma, *cTN* classification was based on endoscopic ultrasonography and/or a CT scan, *TT* transthoracic

* One patient did not have anastomosis

81 %, respectively (Table 5). Predictive factors of OS in pCR patients have been previously studied. Two retrospective studies showed that age and pretherapeutic staging were predictive factors of survival.[11,20] Vallböhmer et al. showed that age was an independent factor of survival in patients with pCR status.[11] We analyzed the same clinicopathologic factors, but we included more clinical details (e.g., clinical stage, ASA score, postoperative complications grades 3–4, dose of radiotherapy, and transfusion). Similarly, age >65 years (HR 2.166; 95 % CI 1.170–4.010; $p = 0.014$) was an independent factor of survival. Furthermore, pretherapeutic stage was not an independent factor of OS and DFS, unlike the results from the retrospective analysis performed by Chao et al.[20] We believe that pretherapeutic stage is important for defining the therapeutic strategy but less so for predicting prognosis after neoadjuvant treatment. A radiation dose <40 Gy (HR 0.361; 95 % CI 0.159–0.820; $p = 0.015$) was an independent factor of survival in the present study. The cutoff of 40 Gy was established in accordance with the CROSS trial.[5] We hypothesized that high-dose radiation may have enhanced postoperative mortality, leading to no survival benefit as suggested recently in the FFCD 9901 trial.[4] Moreover, we speculated that patients with pCR after radiation dose <40 Gy had more favorable biological tumor behavior. No data are available concerning the best dose of radiation, and a randomized controlled study regarding this topic is necessary.

Several studies have analyzed recurrence patterns after neoadjuvant CRT and surgery in patients with esophageal cancer (Table 5). In the present study, the rate of recurrence was 29 % and was comparable to that reported in the current literature (16–39 %). Chao et al. determined that pretreatment was the only factor significantly associated with disease recurrence in 70 patients with pCR status.[20] Our results differed, and clinical stage (cT and cN) did not influence the rate of and time to recurrence. Interestingly, AD histologic subtype (OR 2.008; 95 % CI 0.1.06–0.3.80; $p = 0.032$) was a factor associated with recurrence, unlike the results from the retrospective analysis performed by Zanoni et al. and the CROSS trial.[21, 22] In the CROSS trial, patients with the SCC histologic subtype developed more

locoregional recurrence in the surgery alone arm but not in the CRT plus surgery arm.[22] We hypothesized that the patients with SCC had a higher rate of response to CRT than patients with AD, contributing to decrease recurrence. We believe that it is very difficult to propose the use of adjuvant chemotherapy in patients with a predictive factor of recurrence, particularly in patients with major postoperative complications. No data are available concerning the benefit of adjuvant chemotherapy in patients with pCR. A recent study has suggested a benefit of adjuvant chemotherapy in patients with esophageal AD.[23] However, 50 % of patients could not receive the postoperative regimen and that retrospective study focused on patients without neoadjuvant treatment.

Major postoperative complications were significantly associated with worse survival (HR 2.099; 95 % CI 1.137–3.878; $p = 0.018$) and increased risk of recurrence (OR 2.100; 95 % CI 1.008–4.366; $p = 0.048$). Postoperative complications influenced oncologic outcomes, and this topic was previously examined in several retrospective studies[24–26] Lagarde et al. focused on esophageal AD subtypes and determined that the occurrence of complications was significantly associated with a shorter time interval until death due to recurrence.[24] Similarly, Lerut et al. demonstrated that postoperative complications, according to the Dindo–Clavien classification, were correlated with early recurrence and its timing.[25] We previously studied the effects of postoperative complications on survival in locally advanced esophageal AD treated with neoadjuvant treatment and surgery.[26] Major morbidity was an independent factor of survival. Miyata et al. studied the effect of systemic inflammation on survival in patients with esophageal cancer.[27] They established a systemic inflammation score and demonstrated that it was a major factor significantly associated with survival. We hypothesize that systemic inflammation due to surgery and complications increases the development of microscopic residual disease.[28,29]

This study has some limitations. In both the multivariable and univariable analyses, variables as factors predicting survival and recurrence were uncommon and significant only in multivariable analysis. If there was no significance in the univariable analysis, variables were integrated in the multivariable model when they were relevant in the current literature. However, some data were not integrated in the multivariable model for two reasons. First, some data were unknown (limits of the multicenter retrospective cohort—e.g., malnutrition). Second, the number of patients (56 with recurrence in the present study) limited the number of variables that we integrated in the multivariable analysis. Furthermore, immunohistochemical staining was not systematically performed on sections from patients with pCR who developed

**TABLE 2** Pattern and timing of recurrence

| Location of recurrence | Patients, $n = 191$ (%) | Timing, median [range], (mo) |
|---|---|---|
| Not precise | 3 (1.6) | – |
| Locoregional | 20 (10.5) | 10.5 [0–32] |
| Metastasis | 23 (12.0) | 12 [4–38] |
| Multiple | 10 (5.2) | 23 [4–48] |

**TABLE 3** Univariable and multivariable analyses to identify factors significantly associated with recurrence in the ypT0N0M0 population

| | Univariable analysis | | | Multivariable analysis | | |
|---|---|---|---|---|---|---|
| | OR | 95 % CI | *p* | OR | 95 % CI | *p* |
| Age >65 year | 0.809 | 0.437–1.499 | 0.501 | 1.879 | 0.949–3.731 | 0.070 |
| Gender, male | 0.830 | 0.390–1.765 | 0.628 | | | |
| ASA score 3 | 1.465 | 0.659–3.253 | 0.349 | | | |
| SCC | 1.545 | 0.870–2.746 | 0.138 | 0.498 | 0.263–0.943 | 0.032 |
| cTumor 3 | 1.061 | 0.415–2.714 | 0.901 | 1.809 | 0.533–6.144 | 0.342 |
| cNodes 1 | 1.053 | 0.588–1.886 | 0.861 | 1.471 | 0.714–3.030 | 0.295 |
| Dose <40 Gy | 1.063 | 0.504–2.240 | 0.873 | 1.034 | 0.353–3.030 | 0.952 |
| Location | 0.809 | 0.466–1.405 | 0.452 | | | |
| Thoracotomy | 0.862 | 0.268–2.769 | 0.803 | | | |
| Transfusion | 1.011 | 0.296–3.455 | 0.986 | | | |
| Complications | 0.761 | 0.411–1.408 | 0.384 | 2.100 | 1.008–4.366 | 0.048 |

Univariable and multivariable analysis using Cox regression and the Cox proportional hazards model

*OR* odd ratio, *CI* confidence interval, *ASA* American Society of Anesthesiology, *SCC* squamous cell carcinoma, *cTN* classification was based on endoscopic ultrasonography and/or CT, *Gy* Gray, *Location* infracarinal, *Complications* 3–4 in accordance with the Dindo–Clavien classification system

**TABLE 4** Univariable and multivariable analyses to identify factors significantly associated with survival in the ypT0N0M0 population

| | Univariable analysis | | | Multivariable analysis | | |
|---|---|---|---|---|---|---|
| | HR | 95 % CI | *p* | HR | 95 % CI | *p* |
| Age >65 yr | 0.736 | 0.472–1.149 | 0.178 | 2.166 | 1.170–4.010 | 0.014 |
| Gender, male | 0.657 | 0.350–1.233 | 0.191 | 1.229 | 0.542–2.791 | 0.621 |
| ASA score 3 | 1.220 | 0.701–2.120 | 0.482 | | | |
| SCC | 0.975 | 0.778–1.223 | 0.829 | | | |
| cTumor 3 | 0.999 | 0.723–1.380 | 0.994 | | | |
| cNodes 1 | 0.905 | 0.721–1.135 | 0.387 | | | |
| Dose <40 Gy | 0.513 | 0.244–1.077 | 0.078 | 0.361 | 0.159–0.820 | 0.015 |
| Location | 1.001 | 0.999–1.002 | 0.424 | | | |
| Thoracotomy | 0.757 | 0.481–1.193 | 0.230 | 0.637 | 0.367–1.104 | 0.108 |
| Transfusion | 1.136 | 1.024–1.823 | 0.034 | 0.653 | 0.354–1.204 | 0.172 |
| Complications | 1.282 | 0.774–2.122 | 0.334 | 2.099 | 1.137–3.878 | 0.018 |

Univariable and multivariable analysis using Cox regression and the Cox proportional hazards model

*HR* hazard ratio, *CI* confidence interval, *ASA* American Society of Anesthesiology, *SCC* squamous cell carcinoma, *cTN* classification was based on endoscopic ultrasonography and/or CT, *Gy* Gray, *Location* infracarinal, *Complications* 3–4 in accordance with the Dindo–Clavien classification system

**TABLE 5** Studies with details of survival and recurrence characteristics of pCR patients

| Study and year [reference] | No. of patients | Histology | XRT (Gy) CT | pCR (%) | Survival in pCR | | Recurrence in pCR (%) |
|---|---|---|---|---|---|---|---|
| | | | | | OS 5-year | DSS 5-year | |
| Smit et al. 2013 [18] | 204 | AD: 168<br>SCC: 36 | 41.4<br>Carboplatin<br>Paclitaxel | 25 | 79 % | 79 % | NA |
| van Hagen et al. 2013 [9] | 188 | AD: 107<br>SCC: 80<br>Other: 1 | 40<br>5-FU<br>Cisplatin | 33 | 52 % | 70 % | 39 |
| Zanoni et al. 2013 [21] | 155 | AD: 65<br>SCC: 90 | 50.4<br>Docetaxel<br>5-FU<br>Cisplatin | 41.9 | 72 % | 81 % | 16.9 |
| Meredith et al. 2010 [10] | 347 | AD: 301<br>SCC: 46 | 50.4<br>Cisplatin<br>5-FU | 40.5 | 52 % | 52 % (DFS) | 14.2 |
| Vallböhmer et al. 2010 [11] | 1673 | AD: 181<br>SCC: 118<br>(only pCR) | 40–45<br>5-FU | 18 | 55 % | 68 % | 23.4 |
| Meguid et al. 2009 [19] | 267 | AD: 208<br>SCC: 55<br>Other: 4 | 44<br>5-FU<br>Cisplatin<br>Others | 30.7 | 79 months (median) | 27 (DFS) months (median) | 22 |
| Chao et al. 2009 [20] | 313 | SCC: 313 | 30<br>5-FU<br>Cisplatin | 25 | 59 % | 74 % | 31.4 |

*XRT* radiation dose, *CT* chemotherapy regimen, *pCR* pathological complete response, *OS* overall survival, *DSS* disease-specific survival, *AD* adenocarcinoma, *SCC* squamous cell carcinoma, *FU* fluorouracil, *DFS* disease-free survival

metastases; thus, vital residual tumor cells might have been missed during histopathologic examination. The lack of a standardized pathologic workup might contribute to the variation in the rate of pCR between protocols, resulting in an overestimation of pCR.[15,30] However, histological analysis was performed in the entire surgical specimen in each case of pCR in the current study.

In conclusion, despite a favorable prognosis, one-third of patients with esophageal cancer who achieved pCR after CRT and surgery developed recurrence. The results presented suggest that patients with AD and major postoperative complications have an increased risk of recurrence.

**DISCLOSURE** None declared.

## APPENDIX

The members of the FREGAT (French Eso-Gastric Tumors) working group, FRENCH (Fédération de Recherche EN CHirurgie) and AFC (Association Française de Chirurgie) are given below.

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