

Article

Tumor Regression in Lymph Node Metastases of Esophageal Adenocarcinomas after Neoadjuvant Therapy

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Abstract: Tumor regression following neoadjuvant treatment can be observed in lymph node (LN) metastases similar to the primary tumor in esophageal adenocarcinomas (EAC). We evaluated the prognostic significance of tumor regression in LN metastases of locally advanced EAC of 239 patients treated with neoadjuvant radiochemotherapy (RCTX) or chemotherapy (CTX) followed by esophagectomy. We examined retrospectively the LN for histopathologic signs of regression, i.e., nodular fibrosis and acellular mucin. LN classification was performed according to two parameters: presence (–) or absence (+) of residual tumor and regression characteristics in the LN, resulting in four categories: LN–/REG–, LN–/REG+, LN+/REG+, LN+/REG–. In total, LN metastases with residual tumor were detectable in 117/239 (49%) cases. Regression in LN were observed in 85/239 cases (35.5%). The distribution of the LN/REG categories were as follows: 97 patients (40.6%) were LN–/REG–. A total of 25 patients (10.5%) were LN–/REG+. A total of 60 (25.1%) were LN+/REG+ and 57 (23.8%) LN+/REG–. The LN/Reg categorization had a significant prognostic value in univariate analysis ($p < 0.001$) and multivariate analysis (HR = 1.326; $p = 0.002$) with similar results for the subgroups of patients treated with RCTX or CTX. The prognosis of LN–/REG+ was worse than LN–/REG– but better than both LN+ categories, which was demonstrated in the Kaplan–Meier curves but did not reach statistical significance ($p = 0.104$ and $p = 0.090$, respectively). In contrast, there was no difference between LN+/REG+ and LN+/REG– ($p = 0.802$). In summary, regression in LN metastases of EAC can be observed in a significant number of patients after neoadjuvant therapy. Complete regression of former LN metastases in comparison to “true” negative LN seems to be of prognostic relevance but additional studies are needed to confirm this trend seen in our study.

Keywords: esophagus; adenocarcinoma; regression; lymph node; metastases

1. Introduction

Neoadjuvant chemotherapy (CTX) or radiochemotherapy (RCTX) followed by surgery is standard care for locally advanced esophageal adenocarcinomas, as previous studies have provided evidence

for survival benefit for patients compared to surgery alone [1–6], and both therapy options have been shown to be comparable in the improvement of patient's outcome [7–10]. The morphologic assessment of treatment response is usually performed at the primary tumor site and the degree of regression correlates with long term outcome of the patients [11,12]. Another, if not the most important prognostic factor for esophageal adenocarcinomas (EAC) after neoadjuvant treatment and surgery, is the presence of lymph node metastases (LNM) [13–18]. Tumor regression can be observed in LNM similarly to the primary tumors. Several studies using different, partly rather complex approaches to characterize regressive changes in LN and LNM of esophageal carcinomas have also shown an association between regression of LNM and outcome [19–21].

For gastric cancer, a proposal for a simple categorization of LNM with or without regression has been published [22]. Using a slightly modified categorization system for LN and LNM combining evidence of residual tumor with signs of regression, we recently demonstrated a prognostic impact of regression in LNM in gastric carcinomas (GC), in particular for cases with residual tumor [14].

We now tested whether this categorization system also can be applied in EAC, using well characterized case collections from two surgical centers, where different neoadjuvant therapy procedures (i.e., chemotherapy or radiochemotherapy) were also administered before surgery.

2. Results

2.1. Pathologic Data

According to the TMN classification, 43/239 primary tumors (18%) were described as ypT0, 29 (12.1%) as ypT1, 47 (19.7%) as ypT2, 116 (48.5%) as ypT3 and 4 (1.7%) as ypT4. One hundred twenty-two (51%) of the 239 patients showed tumor free lymph nodes after neoadjuvant therapy (ypN0), while 117 (49%) had LNM with 50 (20.9%) of them categorized as ypN1, 38 (15.9%) ypN2 and 29 (12.1%) ypN3. Distant metastases were present in 24 patients (10%). Complete tumor resection (R0) was achieved in 201/239 cases (81.4%). The tumor regression of the primary tumor according to the tumor regression grade (TRG) system by Becker was classified as TRG1a in 43/239 cases (18%), TRG1b in 78 cases (32.6%), TRG2 in 51 cases (21.3%) and TRG3 in 67 cases (28%; Table 1).

Table 1. Case cohorts and pathological parameters.

Parameter	Total		Cohorts				
			Bern		Munich		
	N	%	N	%	N	%	
ypT category	ypT0	43	18	36	24.5	7	7.6
	ypT1	29	12.1	20	13.6	9	9.8
	ypT2	47	19.7	28	19	19	20.7
	ypT3	116	48.5	59	40.1	57	61.9
	ypT4	4	1.7	4	20.7	0	0
ypN category	ypN0	122	51	87	59.2	35	38
	ypN1	50	20.9	31	21.1	19	20.7
	ypN2	38	15.9	20	13.6	18	19.6
	ypN3	29	12.1	9	6.1	20	21.7
distant Metastases	M0	215	90	136	92.5	79	85.9
	M1	24	10	11	7.5	13	14.1
resection status	R0	201	84.1	138	93.9	63	68.5
	R1/2	38	15.9	9	6.1	29	31.5
neoadjuvant therapy	CTX	114	47.7	22	15	92	100
	RCTX	125	52.3	125	85	0	0

Table 1. Cont.

Parameter	Total		Cohorts				
	N	%	Bern		Munich		
			N	%	N	%	
TRG (Becker) primary tumor	1a	43	18	36	24.5	7	7.6
	1b	78	32	56	38.1	22	23.9
	2	51	21.3	25	17	26	28.3
	3	67	28	30	20.4	37	40.2
LN category	LN-/REG-	97	40.6	69	46.9	28	30.4
	LN-/REG+	25	10.5	18	12.2	7	7.6
	LN+/REG+	60	25.1	36	24.5	24	26.1
	LN+/REG-	57	23.8	24	16.3	33	35.9

2.2. Regressive Changes in Lymph Nodes

In total, vital LNM (ypN1-3) were found in 117/239 (49%) cases after neoadjuvant therapy. The number of resected and examined LN ranged from 5 to 86 (median = 25). Regressive changes in LN were observed in 85/239 cases (35.5%). Using the proposed categorization, 97 patients (40.6%) had negative LN without regression (LN-/REG-). A total of 25 (10.5%) had completely regressed LNM (LN-/REG+), 60 (25.1%) persistent LNM with regression (LN+/REG+) and 57 (23.8%) had LNM without evidence of regression (LN+/REG-; Table 1).

2.3. Correlation with Pathological Data

A major response of the primary tumor correlated with the categorization of LN/LNM described above. 19/25 of the cases (76%) with complete LN regression (LN-/REG+) could also be graduated with TRG1a or TRG1b with decreasing prevalence for LN+/REG+ (21/60; 35%) and for LN+/REG- (11/60; 19.3%). However, some cases also showed different responses in LNM and primary tumor. A total of 6/25 patients (24%) with completely regressed LNM showed a poor primary tumor response (TRG2 or TRG3). A total of 43 of 85 cases with presence of LN regression (50.6%), 4 of them with complete LN regression, showed TRG2 or TRG3. Among the LN+/REG- category, however, no case with complete regression of the primary tumor (TRG1a) was observed (Table 2).

Table 2. Lymph node (LN) categories and Tumor Regression Grades of the primary tumors.

	LN category	TRG (Becker)				Total
		1a	1b	2	3	
	LN-/REG-	32	38	17	10	97
	LN-/REG+	7	12	2	4	25
	LN+/REG+	4	17	16	23	60
	LN+/REG-	0	11	16	30	57
	total	43	78	51	67	239

2.4. Survival Analysis

Survival data were available for 226/239 patients. With regard to overall survival, the LN/REG categorization was a prognostically significant parameter in univariate analysis. Patients with negative nodal status after neoadjuvant therapy, regardless of regression status (i.e., LN-/REG- or LN-/REG+), had significantly better survival ($p < 0.001$) than patients with LN+/REG+ and LN+/REG- combined. Between the categories LN-/REG- and LN-/REG+, which are summarized as ypN0 in the TNM classification, a trend for a better survival for the former was observed, but without statistical significance ($p = 0.104$). The LN-/REG+ group, which comprised only 25 patients, however, also showed a trend

for a better survival compared to LN+ patients, regardless of regression ($p = 0.090$). No difference was found between LN+/REG+ and LN+/REG- ($p = 0.802$; Figure 1).

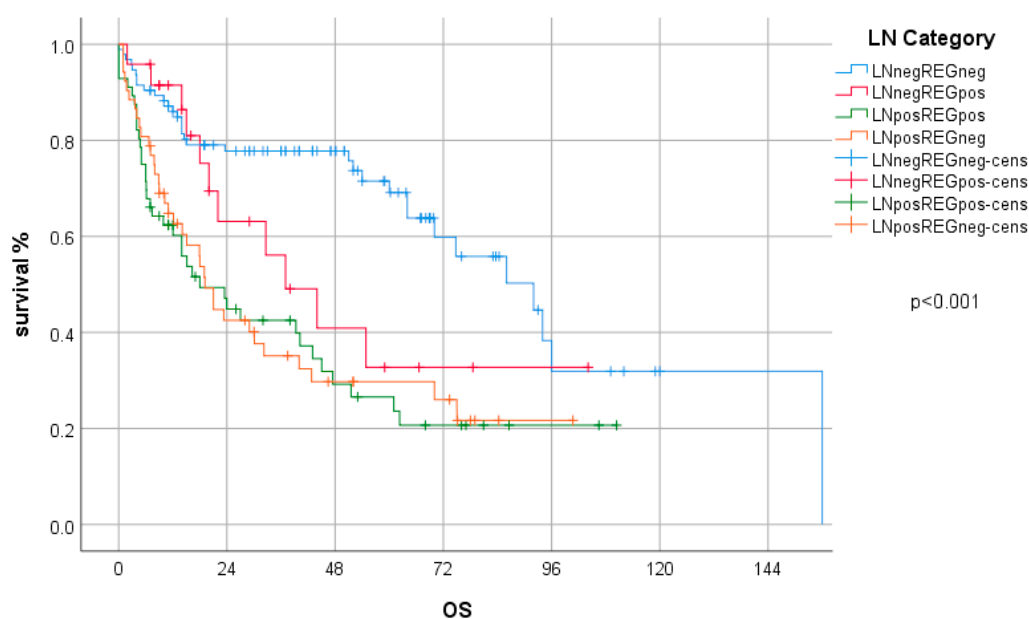


Figure 1. LN categories and overall survival (OS).

Other prognostically relevant factors in univariate analyses were TRG according to Becker, ypT-category, ypN-category, ypM-category (each $p < 0.001$) and resection status ($p = 0.031$).

The LN/REG categorization was also an independent prognostic factor in a multivariate analysis (Hazard ratio (HR) = 1.32; 95% CI 1.11–1.58; $p = 0.002$), including TRG, ypT category, distant metastases and resection status (Table 3). The HR and significance levels for the LN/REG categorization were similar to those of the ypN categories according to the TNM classification, which also proved to be an independent prognostic parameter in multivariate analysis including the same influencing variables as mentioned above (HR = 1.28; 95% CI 1.05–1.57; $p = 0.016$).

Table 3. Multivariate Analysis.

	HR	95% CI for HR		p-Value
		Lower	Upper	
ypTcategory	1.118	0.874	1.430	0.376
TRG (Becker)	1.094	0.845	1.417	0.496
LN category	1.324	1.108	1.583	0.002
distant metastases	2.492	1.412	4.400	0.002
resection status	0.754	0.444	1.280	0.295

2.5. Subgroup Analysis—Case Collections and Type of Neoadjuvant Treatment

The two case collections differed regarding the following parameters: in the Bern cohort, radiochemotherapy was the predominantly used neoadjuvant therapy regime, while in the Munich cohort only neoadjuvant chemotherapy was used ($p < 0.001$). Although the number of patients who achieved complete regression of the primary tumor was significantly higher in the Bern cohort ($p < 0.001$), the overall survival did not significantly differ ($p = 0.537$). This was also the case for the comparison between neoadjuvant RCTX and CTX, the latter group also including cases from Bern: neoadjuvant RCTX was associated with a higher rate of complete regression of the primary tumor ($p < 0.001$) but not with overall survival ($p = 0.223$). Regarding the LN/REG categories, in the Bern cohort and the RCTX group, the percentage of LN-/REG- and LN-/REG+ cases was higher compared

to the Munich cohort and the CTX group, respectively ($p = 0.003$; and $p = 0.002$). The overall prognostic impact for the LN/REG categorization was significant in all subgroups (Bern cohort: $p < 0.001$; Munich cohort: $p = 0.011$; RCTX group: $p = 0.001$; CTX group: $p = 0.003$), which was also seen in the multivariate analyses (Bern cohort: HR = 1.19; 95%CI = 0.938–1.510; $p = 0.152$; Munich cohort: HR = 1.484; 95%CI = 1.122–1.962 $p = 0.006$; RCTX group: HR = 1.197; 95%CI = 0.912–1.570 $p = 0.195$; CTX group: HR = 1.452; 95%CI = 1.132–1.862; $p = 0.003$; for details see Table 1 and supplemental data Figures S1–S4 and Tables S1–S4).

3. Discussion

We investigated the impact of regressive changes in lymph nodes (LN) or LN metastases (LNM), in particular, on survival in locally advanced esophageal adenocarcinomas (EAC) after neoadjuvant chemo- or radiochemotherapy (CTX or RCTX) using a dichotomous classification of two parameters, according to which the LN were categorized by presence or absence of residual metastases (LN– or LN+) and regression characteristics (REG– or REG+).

We observed regressive changes in approximately 30%—among them complete regression of previous metastases in occurred 10% of the total number of patients. On the other hand, there was total absence of regressive changes in LN metastases in 25% of the cases. We observed a significant positive correlation between the regression of the primary tumors and the LN metastases. Moreover, we demonstrated, that the group of patients with truly negative nodal status (LN–/REG–) as well as those with complete regression of previous LN metastases (LN–/REG+) had a better overall survival than those cases with residual metastases in the LN, regardless of whether with or without regressive changes (LN+/REG+ or LN+/REG–). However, occurrence of regressive changes in the subgroups of both ypN0 and ypN+ patients did not result in a significant survival benefit taking these groups alone. The prognosis of LN–/REG+ was worse than LN–/REG– but better than both LN+ categories, which was clearly seen in the Kaplan–Meier curves but did not reach statistical significance ($p = 0.104$ and $p = 0.090$, respectively). Therefore, the ypN status proved to be the most prognostically relevant parameter in our study.

According to previously published work, tumor shrinkage, fibrosis, acellular mucin, histiocytic reaction with foamy macrophages, calcification, necrotic areas have been suggested as main histopathological signs of regressive changes after neoadjuvant therapy [23,24]. The histopathological characteristics of regressive changes (e.g., fibrosis, necrosis, acellular mucin, histiocytic reactions and calcification) are the same for primary tumors and lymph nodes. We defined central fibrosis and acellular mucin as characteristic for regression. However, fibrosis cannot only be considered a therapeutic consequence of chemoradiotherapy but it can also be interpreted as a consequence of other non-specific inflammatory reactions [25–28]. Even in patients who have not received chemoradiotherapy, fibrosis can occur in the sense of a body's own defensive reaction to tumor cells. However, it has been demonstrated before that the interobserver agreement for the determination of regressive changes in LNM is within substantial levels [13,29].

In upper gastrointestinal cancers LN staging has a very high prognostic value [14]. For tumors treated with multimodal therapy, previous studies postulated that, not only the ypN status, but also the additional reporting and categorization of lymph node metastasis regression, may have important prognostic value [13,23,29–34].

Different approaches on the classification of regressive changes have been described. Bollschweiler et al. [35] introduced a classification with three grades: low risk (no LN metastasis and fewer than three LNs with central fibrosis), medium risk (no LN metastasis and central fibrosis in three or more LNs, or LN metastasis with a LN ratio of less than 0.05) and high risk (all other cases). A previous study of our group on gastric cancer [29] proposed a dichotomous classification, which focused only on the assessment of whether regression was present in any of the investigated lymph nodes. This system had been proposed by an expert panel for the application in gastric cancer [22]. We therefore decided to apply this system on the esophageal adenocarcinoma cohort, also allowing a direct comparison to

the cohort of gastric carcinomas reported previously. The frequency of regressive changes of about 30% in LN metastases of a patient in our study is comparable to other studies, both for esophageal and gastric cancer [13,23,29,36]. One study by Zhu et al. [37], however, reported a probability of occurrence of about 64%, which is as twice as much compared to other studies. Similarities of this work with our study are the use of the same classification and the size of the patient population studied. Differences are the entity of the primary tumor (stomach vs. esophagus) and the ethnic background of the patients, which would explain this outstanding difference, compared to other studies.

The majority of studies on gastric and esophageal carcinomas agree on the prognostic significance of the presence or absence of LN metastases: Patients with ypN0, whether with or without regression in their LN metastases, have a clear survival advantage compared to patients with ypN+ [13,23,29,31,35,37,38].

Moreover, there are several studies that suggest that regression following neoadjuvant treatment may also have a prognostic value: in a subsequent work, Bollschweiler et al. were able to demonstrate that cases with metastasis-free LN and less than three regression features in terms of central fibrosis have a significantly better survival than those with more than three central fibrosis or even vital LN metastases [31,35]. They conclude that regressively altered LN seem to be former metastases and that, with respect to the LN- group, an increasing number of regressive lymph nodes additionally worsens survival. It is hypothesized that with increasing number of LN metastases, whether vital or regressive, the probability of micrometastases increases, which may explain the deterioration in overall survival. The fact, however, that this type of classification combines “true” ypN0 patients with “false” ypN0 patients (i.e., former N+ patients) in one tier impedes a clear differentiation regarding the prognosis of these two collectives. Likewise, studies in line with our classification did not achieve the establishment of significant prognostic differences between the cases with LN-/REG- and LN-/REG+. Nieman et al. [23] suggest that patients with former LN metastases with complete regression should be staged as ypN+, because LN with complete regression have a comparable negative influence on survival to positive LN. This, in turn, confirms the necessity of introducing a classification for lymph node staging that also takes regression into account.

In gastric cancer [29], but in contrast to this study on esophageal adenocarcinomas, we were able to demonstrate a significant prognostic advantage of the presence over absence of regressive changes in nodal positive patients. Since this was observed both in the RCTX and the CTX group, the tumor entity rather than the type of neoadjuvant treatment may be responsible for this difference.

The study has some limitations. First, it is a retrospective analysis and not associated to a clinical trial. Second, the cases collections generated from historical cohorts and novel treatment approaches may have a different effect on regression of the primary tumors and metastases. Third, we did not record the number of affected or regressed LNM, respectively. According to some studies, this factor plays an important role in estimating the prognosis of a patient, especially in ypN0 cases. In our study, however, a classification was used that does not consider the number of regressive changes—this may be much more practical in terms of cost and benefit and clinical consequence, which becomes increasingly important in medicine.

Lastly, the number of patients with former, post-therapeutically, completely regressed LN was rather low. This may explain the lack of significance levels in the comparison to the LN-/REG- and LN+ groups despite a clear visible trend in the Kaplan—Meier curves. Since these trends go in line with the results of other studies, we conclude that the detection of a former LNM separates a patient from those who had always tumor free LN and that this warrants the report of regressive changes or the description of a completely regressed LNM in pathological reports. Interestingly, in the group of LN+ patients however, our results do not show a survival benefit of regression when there is still residual tumor detectable.

In summary, our data show that tumor regression of LN metastases can be observed in a substantial number of EAC after neoadjuvant therapy. The most relevant prognostic impact may be observed in the group of patients with former LN metastases that have completely regressed but should not be staged as simple ypN0. Reporting of regressive changes in LN, or LN metastases, respectively,

should be integrated in pathology reports of upper gastrointestinal cancers which is already performed by a substantial number of gastrointestinal pathologists according to a recent survey [39].

4. Materials and Methods

4.1. Patients

The study included a total of 239 patients with locally advanced adenocarcinoma of the esophagus (EAC) as defined by the WHO classification [40] who were treated with neoadjuvant chemotherapy or chemoradiotherapy. Both collectives have been described in detail before and differed in their therapeutic approach [41,42]: The first collective comprised 92 cases, treated between 1994 and 2002 in the department of surgery of the Technische Universität München, Munich [42]. Neoadjuvant treatment consisted of a cisplatin/5-fluorouracil/Leucovorine-based chemotherapy with or without additional paclitaxel. Surgical resection of the tumors was performed by transmediastinal or transthoracic (Ivor Lewis) esophagectomy.

The second collective comprised 147 patients, treated between 2001 and 2016 at the department of Surgery of the Inselspital University Hospital Bern [41]. Neoadjuvant treatment was predominantly composed of combined radiation with at least 40 gray and a 5-fluorouracil and Cisplatin/Carboplatin-based chemotherapy with or without additional Paclitaxel or Docetaxel. Neoadjuvant treatment was followed by transmediastinal esophageal resection with a radical bilateral mediastinal en-bloc lymphadenectomy.

Patient data were taken from prospectively managed databases. Follow-up included endoscopy and CT scans at intervals of 6 to 12 months over at least 5 years according to institutional protocols. Survival was computed from the day of surgery. More details of the patient groups can be found in Table 1. The usage of pathologic and clinical data for research had been approved by the ethics committees of the Medical Faculty of the Technische Universität München, 2056/08 and the Canton of Bern, 2017-01623.

4.2. Post Neoadjuvant TNM Staging and Tumor Regression Grading

Histopathological examination of the resection specimens and the assessment of TNM categories was performed as described before [41–43]. Data for histopathological tumor regression according to Becker (Tumor regression grade (TRG) 1a = complete regression; TRG1b = <10% residual tumor; TRG2 = 10–50% residual tumor; TRG3 = >50% residual tumor) and determined by experienced pathologists with a special focus on gastrointestinal tumors (KB, RL) were obtained from previous studies [41,42] or generated for the purpose of the present work.

4.3. Evaluation of Tumor Regression in Lymph Node Metastases

The lymph nodes (LN) of all 239 cases were examined for histopathological features of regression by three observers (KB, RL, MO). The presence of hyaline fibrosis, acellular mucin or sheets of foamy histiocytes were defined as characteristic for therapy induced regression (Figure 2), in line with previous reports [23,24,29]. We then applied the categorization system, which was already described for gastric cancer [22,37]: it distinguishes between the presence and absence of regression (REG– or REG+) in LN along with the absence or presence of residual tumor (LN– or LN+), regardless of the number of affected LN and without further graduation regarding the extent of regression or number of regressed LNM [13,31]. By combining these items, the following categories can be defined: LN–/REG–: ypN0 category without signs of regression; LN–/REG+: ypN0 category with evidence of regression; LN+/REG+: ypN1-3 categories with evidence of regression; LN+/REG–: ypN1-3 categories without signs of regression.

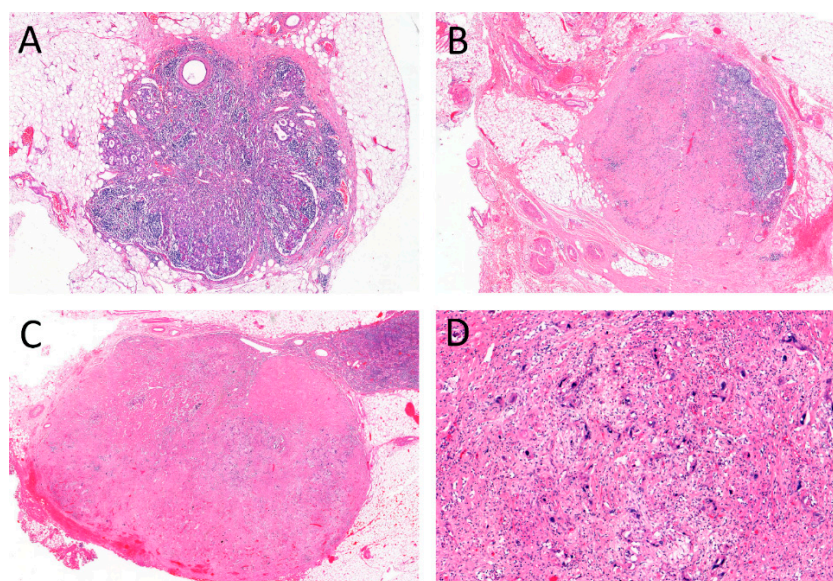


Figure 2. Examples of lymph node metastases (LNM): (A) LNM without regression (LN+/REG−); (B) LN with completely regressed former metastasis (LN−/REG+); (C) LNM with regression and residual tumor (LN+/REG+); higher magnification of (C); all images magnification $\times 10$, except (D) ($\times 40$).

4.4. Statistical Analysis

The statistical analyses were carried out using IBM SPSS Statistics 26 (IBM Corporation, Armonk, NY, USA). Comparisons between groups and categories were made performed using cross tables, χ^2 tests, and Fisher's exact tests. Survival analysis included Kaplan–Meier curves and log-rank tests for univariate survival analysis and Cox regression analysis (enter method) for multivariate analysis. p -values of <0.05 were considered significant for all statistical tests.

Supplementary Materials: The following are available online at <http://www.mdpi.com/2624-5647/2/4/36/s1>, Figure S1: Bern cohort: LN categories and overall survival Table S1: Bern cohort: multivariate analysis, Figure S2 Munich cohort: LN categories and overall survival, Table S2: Munich cohort: multivariate analysis, Figure S3: RCTX patients and overall survival, Table S3: RCTX patients: multivariate analysis, Figure S4: CTX patients and overall survival, Table S4: CTX patients: multivariate analysis.

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