The Assessment of Risk Factors for Long-term Survival Outcome in ypN0 Patients With Rectal Cancer After Neoadjuvant Therapy and Radical Anterior Resection

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Research

Keywords: stage migration, rectal cancer, lymph node yield, Charlson comorbidity index, late anastomotic leakage, anterior rectal resection

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Abstract

Background: The main negative prognostic factors in patients with rectal cancer after radical treatment include regional lymph node involvement, lymphovascular invasion, perineural invasion, the mucinous component of the tumor and poor differentiation. However, some patients still develop cancer recurrence despite the absence of the above risk factors.

The aim of the study was to assess clinicopathological factors influencing long-term oncologic outcomes in ypN0M0 rectal cancer patients after neoadjuvant therapy and radical anterior rectal resection.

Methods: A retrospective survival analysis was performed on a group of 195 patients treated between 2008 and 2016. We assessed clinicopathological factors which included tumor regression grade, number of lymph nodes in the specimen, Charlson comorbidity index (CCI), and colorectal anastomotic leakage (AL).

Results: In the univariate analysis, AL and CCI> 3 had a significant negative impact on disease-free survival (DFS), disease-specific survival (DSS), and overall survival (OS). After the division of ALs into early and late ALs, it was found that only patients with late ALs had a significantly worse survival. The multivariate Cox regression analysis showed that CCI> 3 was a significant adverse risk factor for DFS (HR:5.78, 95%CI:2.15-15.51, p<0.001), DSS (HR:7.25, 95%CI:2.25-23.39, p<0.001), and OS (HR:3.9, 95%CI:1.72-8.85, p=0.001). Similarly, late ALs had a significant negative impact on the risk of DFS (HR:5.05, 95%CI:1.97-12.93, p<0.001), DSS (HR:10.84, 95%CI:3.44-34.18, p<0.001) and OS (HR:4.3, 95%CI:1.94-9.53, p<0.001).

Conclusions: Late AL and CCI> 3 are the factors that may have an impact on long-term oncologic outcomes. The impact of lymph node yield on understaging was not demonstrated.

Background

Long-term treatment results of rectal cancer patients after the introduction of combined treatment regimens and the techniques of total mesorectal excision have significantly improved. After neoadjuvant therapy and radical surgery, negative prognostic factors include regional lymph node involvement and a number of histopathological factors related to the potential for tumor invasiveness, such as lymphovascular invasion (LVI), perineural invasion (PNI), poor differentiation or the mucinous component of the tumor [1]. However, even some ypN0M0 patients with no additional histopathological risk factors have a relapse. Several studies showed a negative impact of colorectal anastomotic leakage (AL) on long-term survival after anterior rectal resection (AR) [2, 3]. However, such findings were not confirmed in all studies [4]. Additionally, the minimum number of lymph node yield (LNY) that could allow to avoid understaging in ypN0 patients has not been established either. Research found either a negative impact [5, 6] or no impact [7, 8] of low LNY on long-term oncologic outcomes. The influence of preoperative radiotherapy on the reduction in the number of resected lymph nodes was also demonstrated [9]. Some studies found that low LNY was associated with a good response to neoadjuvant therapy [10]. Few

studies suggested that apart from the effect associated with increased mortality due to comorbidities, their direct impact on the course of the neoplastic disease was possible. However, the mechanism of this interaction has not been fully understood yet [11].

The aim of the study was to assess the selected clinicopathological factors influencing long-term oncologic outcomes in ypN0M0 rectal cancer patients after neoadjuvant therapy and radical AR in the group of patients with a good prognosis without major histological risk factors.

Methods

Between 2008 and 2016, 328 radical (R0) ARs were performed at the National Research Institute of Oncology in Gliwice, Poland in rectal cancer patients after neoadjuvant therapy without synchronous distant metastases. Metastases that occurred within 3 months after surgery were considered synchronous. Prior to treatment, all patients had been staged T3N0 or T1-3N+. Five patients who died within 30 postoperative days were excluded from further analysis. To select the group with a good prognosis, we also excluded ypN + patients (n = 119), subjects with the mucinous component (n = 3), and with the presence of PNI and/or LVI (n = 6) found in the histopathological examination. Finally, 195 patients (82 females, 113 males) without the above risk factors were enrolled in a retrospective study. Patient characteristics are given in Table 1. All patients were given neoadjuvant therapy, i.e., radiotherapy (RT) or chemoradiotherapy (CRT). In the RT group, the total dose was 25–42 Gy, while in the CRT group it was 42–54 Gy combined with one or two cycles of 5-fluorouracil-based chemotherapy. The procedure was performed by laparotomy using the mesorectal excision technique. End-to-end intestinal anastomosis was performed with a circular stapler. According to the International Study Group of Rectal Cancer, AL was defined as a defect of the intestinal wall at the anastomotic site, which resulted in a communication between the intra- and extraluminal compartments and/or the presence of a pelvic abscess near the anastomotic site [12]. AL diagnosed within 30 days postoperatively was considered early, whereas AL diagnosed after 30 days postoperatively was regarded as late. The severity of comorbidities was assessed based on the original Charlson comorbidity index (CCI). [13]. The tumor response to preoperative treatment ranged from 0 (complete response), 1 (moderate response), 2 (poor response) to 3 (no response to treatment). The factors which were analyzed in terms of their impact on survival included sex, age, body mass index (BMI), body surface area (BSA), CCI, clinical stage prior to treatment, type of neoadjuvant therapy (RT vs CRT), time from RT to surgery, rectal tumor location, loop ileostomy (LI), G, ypT, LNY, TRG, width of the distal margin, length of the resected intestine, occurrence of AL with the division into early and late ALs, and post-surgical adjuvant chemotherapy. The survival analysis was performed using the Kaplan-Meier method with the log-rank test. The multivariate analysis was performed using the Cox regression (proportional hazard model).

Table 1
Patient characteristics

		Total (N = 195)
Sex	Females	42.1% (N = 82)
	Males	57.9% (N = 113)
Age	Mean (SD)	63.96 (10.03)
	Median (IQR)	65 (58–72)
	Range	26–84
BMI (kg/m^2)	Mean (SD)	26.21 (4.03)
	Median (IQR)	25.8 (23.85–28.4)
	Range	17.5–38.5
BMI > 30 (kg/m^2)	Yes	15.9% (N = 31)
	No	84.1% (N = 164)
BSA (m^2)	Mean (SD)	1.85 (0.21)
	Median (IQR)	1.85 (1.68–2)
	Range	1.32–2.38
CCI	2	72.8% (N = 142)
	3	21.6% (N = 42)
	> 3	5.6% (N = 11)
Clinical stage prior to treatment	II	29.7% (N = 58)
	III	70.3% (N = 137)
Neoadjuvant therapy	RT	65.1% (N = 127)
	CRT	34.9% (N = 68)
Time RT-S ≥ 6 weeks	Yes	54.9% (N = 107)
	No	45.1% (N = 88)
Rectal tumor location, distance from the anal verge (cm)	Upper (11–15)	23.1% (N = 45)
	Middle (6–10)	47.7% (N = 93)

SD- standard deviation, IQR- interquartile range, BMI- body mass index, BSA- body surface area, CCI- Charlson comorbidity index, RT- radiotherapy, CRT- chemoradiotherapy, Time RT-S- time from completion of radiotherapy to surgery, LNY- lymph node yield, TRG- tumor regression grade, AL- anastomotic leakage

		Total (N = 195)
	Low (1–5)	29.2% (N = 57)
Loop ileostomy	Yes	21% (N = 41)
	No	79% (N = 154)
G	1	8.2% (N = 16)
	2	57.2% (N = 111)
	X	34.5% (N = 67)
ypT	0	8.7% (N = 17)
	1–2	50.3% (N = 98)
	3	41% (N = 80)
LNY	Mean (SD)	12.15 (6.01)
	Median (IQR)	11 (8–16)
	Range	1–37
LNY groups	1–7	23.1% (N = 45)
	8–12	36.9% (N = 72)
	> 12	40% (N = 78)
Width of the distal margin (cm)	Mean (SD)	2.13 (1.41)
	Median (IQR)	2 (1–3)
	Range	0.1–9
Width of the distal margin < 2cm	Yes	46.7% (N = 91)
	No	53.3% (N = 104)
Length of the resected intestine (cm)	Mean (SD)	19.54 (4.81)
	Median (IQR)	20 (16–22)
	Range	7–35
TRG	0–1	46.7% (N = 91)
	2–3	53.3% (N = 104)

SD- standard deviation, IQR- interquartile range, BMI- body mass index, BSA- body surface area, CCI- Charlson comorbidity index, RT- radiotherapy, CRT- chemoradiotherapy, Time RT-S- time from completion of radiotherapy to surgery, LNY- lymph node yield, TRG- tumor regression grade, AL- anastomotic leakage

		Total (N = 195)
Anastomotic leakage (AL)	No	81% (N = 158)
	Early	11.3% (N = 22)
	Late	7.7% (N = 15)
Adjuvant chemotherapy	Yes	8.2% (N = 16)
	No	91.8% (N = 179)

SD- standard deviation, IQR- interquartile range, BMI- body mass index, BSA- body surface area, CCI- Charlson comorbidity index, RT- radiotherapy, CRT- chemoradiotherapy, Time RT-S- time from completion of radiotherapy to surgery, LNY- lymph node yield, TRG- tumor regression grade, AL- anastomotic leakage

Results

AL was postoperatively found in 37/195 (19%) cases, including 22/37 (59.5%) early and 15/37 (40.5%) late ALs. Four patients with early ALs (4/22; 18.2%) and 2 patients with late ALs (2/15; 13.3%) underwent loop ileostomy (LI) at the time of primary surgery (Chi2 test, p = 0.7). The time from surgery to the diagnosis of early and late ALs was 3–27 days (mean 7.7 days) and 36–650 days (mean 137 days), respectively. The mean LNY was 12.15 (range 1–37, SD: 6.01) and the median was 11 (IQR: 8–16). The mean follow-up of the study group was 69 months. The 3- and 5-year DFS rates were 89% and 85.7%, 3- and 5-year DSS rates were 97.9% and 93.4%, whereas 3- and 5-year OS rates were 91.3% and 84.8%, respectively.

In the univariate analysis of survival, the occurrence of AL had a significant impact on DFS, DSS and OS, as shown by the log-rank test. After the division of ALs into early and late ALs, it was found that only patients with late ALs had a significantly worse prognosis. The probability of survival depending on the occurrence of AL is given in Fig. 1. Patients with CCI $\leq$ 3 had a significantly better prognosis compared to patients with CCI > 3 in terms of DFS, DSS, and OS. The probability of survival depending on CCI is given in Fig. 2. Table 2 lists the 3- and 5-year survival probabilities depending on the above factors. No relationship was found between survival and other parameters, including LNY. The probability of survival depending on LNY is given in Fig. 3.

Table 2
3- and 5-year survival probabilities depending on the parameters significant in the univariate analysis

	DFS		DSS		OS	
	3-year %	5-year %	3-year %	5-year %	3-year %	5-year %
No AL	90.8	88.9	99.3	95.3	93.7	88.4
AL	80.9	71.2	91.5	84.3	81.1	68.6
Early AL	88.8	81.4	95.2	89.3	81.8	72.2
Late AL	70.7	56.6	85.7	77.9	80.0	63.6
CCI ≤ 3	90.2	87.4	98.3	94.7	92.4	86.0
CCI > 3	67.5	56.2	80.0	70.0	72.7	63.6

DFS- disease-free survival, DSS- disease-specific survival, OS- overall survival, AL- anastomotic leakage, CCI- Charlson comorbidity index

The results of the univariate and multivariate Cox regression analyses are presented in Table 3. In the multivariate analysis, CCI > 3 was a significant risk factor for DFS (HR:5.78, 95%CI:2.15–15.51, $p < 0.001$), DSS (HR:7.25, 95%CI:2.25–23.39, $p < 0.001$), and OS (HR:3.9, 95%CI:1.72–8.85, $p = 0.001$). Similarly, the occurrence of late AL had a significant negative impact on the risk of DFS (HR:5.05, 95%CI:1.97–12.93, $p < 0.001$), DSS (HR:10.84, 95%CI:3.44–34.18, $p < 0.001$) and OS (HR:4.3, 95%CI:1.94–9.53, $p < 0.001$). No significant influence of early AL or other factors on long-term survival was found.

Table 3
Results of univariate and multivariate Cox regression analyses

		Univariate				Multivariate			
		HR	CI 2.5%	CI 97.5%	P	HR	CI 2.5%	CI 97.5%	p
DFS	CCI ≤ 3	Ref.							
	CCI > 3	5.438	2.043	14.48	**< 0.001**	5.779	2.153	15.51	**< 0.001**
	Female	Ref.							
	Male	2.19	0.9255	5.184	0.0744				
	BMI ≤ 30	Ref.							
	BMI > 30	1.885	0.7968	4.459	0.1491				
	PRETR ST II	Ref.							
	PRETR ST III	0.6896	0.3156	1.506	0.3512				
	RT-S < 6weeks	Ref.							
	RT-S ≥ 6weeks	0.8681	0.4	1.884	0.7205				
	Distance 1-5cm	Ref.							
	6-10cm	0.6141	0.2494	1.512	0.2889				
	11-15cm	1.269	0.4858	3.313	0.6269				
	No ileostomy	Ref.							
	Ileostomy	1.04	0.4192	2.58	0.9327				
	ypT0	Ref.							
	ypT1-2	1.888	0.2451	14.55	0.5417				
	ypT3	3.031	0.3978	23.1	0.2845				
	LNY 1–7	Ref.							

Bold values indicate statistical significance

DFS- disease-free survival, DSS- disease-specific survival, OS- overall survival, HR- hazard ratio, CI- confidence interval, CCI- Charlson comorbidity index, BMI- body mass index, PRETR ST- pretreatment clinical stage, RT- radiotherapy, LNY- lymph node yield, TRG- tumor regression grade, AL- anastomotic leakage, RT-S- time from completion of radiotherapy to surgery, Adj CT- adjuvant chemotherapy

		Univariate				Multivariate			
	LNY 8–12	2.106	0.5791	7.66	0.2581				
	LNY > 12	3.106	0.8916	10.82	0.0751				
	Distal margin (cm)	1.034	0.7951	1.344	0.8051				
	TRG 0–1	Ref.							
	TRG 2–3	1.156	0.5409	2.469	0.7087				
	No AL	Ref.							
	AL	3.066	1.403	6.702	**0.005**				
	No AL	Ref.							
	Early AL	2.001	0.6725	5.953	0.2125	1.96	0.6587	5.831	0.2265
	Late AL	4.753	1.87	12.08	0.0011	5.051	1.974	12.93	**< 0.001**
	No adj CT	Ref.							
	Adj CT	0.695	0.1632	2.959	0.6225				
DSS	CCI ≤ 3	Ref.							
	CCI > 3	5.39	1.754	16.56	**0.0033**	7.252	2.249	23.39	**< 0.001**
	Female	Ref.							
	Male	1.543	0.54	4.41	0.418				
	BMI ≤ 30	Ref.							
	BMI > 30	2.141	0.7526	6.089	0.1536				
	PRETR ST II	Ref.							
	PRETR ST III	0.643	0.2443	1.692	0.3711				
	RT-S < 6weeks	Ref.							
	RT-S ≥ 6weeks	1.145	0.4126	3.175	0.7954				

Bold values indicate statistical significance

DFS- disease-free survival, DSS- disease-specific survival, OS- overall survival, HR- hazard ratio, CI- confidence interval, CCI- Charlson comorbidity index, BMI- body mass index, PRETR ST- pretreatment clinical stage, RT- radiotherapy, LNY- lymph node yield, TRG- tumor regression grade, AL- anastomotic leakage, RT-S- time from completion of radiotherapy to surgery, Adj CT- adjuvant chemotherapy

		Univariate				Multivariate			
	Distance 1-5cm	Ref.							
	6-10cm	0.5699	0.1834	1.771	0.3309				
	11-15cm	1.458	0.4378	4.855	0.5392				
	No ileostomy	Ref.							
	Ileostomy	1.311	0.4259	4.037	0.6367				
	ypT0	Ref.							
	ypT1-2	0.7613	0.0883	6.565	0.804				
	ypT3	2.153	0.2754	16.83	0.4648				
	LNY 1–7	Ref.							
	LNY 8–12	1.605	0.3207	8.033	0.5648				
	LNY > 12	2.267	0.4854	10.59	0.2979				
	Distal margin (cm)	1.052	0.7511	1.473	0.7688				
	TRG 0–1	Ref.							
	TRG 2–3	1.202	0.4539	3.183	0.7112				
	No AL	Ref.							
	AL	3.218	1.222	8.476	**0.018**				
	No AL	Ref.							
	Early AL	1.245	0.2705	5.73	0.7785	1.543	0.3303	7.21	0.5812
	Late AL	8.519	2.825	25.69	**< 0.001**	10.84	3.435	34.18	**< 0.001**
	No adj CT	Ref.							
	Adj CT	0.4898	0.0642	3.735	0.4911				
OS	CCI ≤ 3	Ref.							

Bold values indicate statistical significance

DFS- disease-free survival, DSS- disease-specific survival, OS- overall survival, HR- hazard ratio, CI- confidence interval, CCI- Charlson comorbidity index, BMI- body mass index, PRETR ST- pretreatment clinical stage, RT- radiotherapy, LNY- lymph node yield, TRG- tumor regression grade, AL- anastomotic leakage, RT-S- time from completion of radiotherapy to surgery, Adj CT- adjuvant chemotherapy

	Univariate				Multivariate			
CCI > 3	3.494	1.553	7.859	**0.0025**	3.899	1.718	8.85	**0.0011**
Female	Ref.							
Male	0.984	0.5321	1.82	0.9591				
BMI ≤ 30	Ref.							
BMI > 30	0.9914	0.441	2.229	0.9833				
PRETR ST II	Ref.							
PRETR ST III	0.6993	0.3791	1.29	0.2522				
RT-S < 6weeks	Ref.							
RT-S ≥ 6weeks	0.642	0.334	1.234	0.1836				
Distance from the anal verge 1-5cm	Ref.							
6-10cm	0.5456	0.281	1.06	0.0736				
11-15cm	0.7257	0.3136	1.679	0.4538				
No ileostomy	Ref.							
Ileostomy	1.113	0.5326	2.326	0.7758				
ypT0	Ref.							
ypT1-2	1.258	0.2893	5.466	0.7598				
ypT3	2.332	0.5488	9.905	0.2514				
LNY 1–7	Ref.							
LNY 8–12	0.8853	0.3847	2.037	0.7746				
LNY > 12	1.064	0.4784	2.365	0.8798				
Distal margin (cm)	1.057	0.8581	1.301	0.6039				
TRG 0–1	Ref.							

Bold values indicate statistical significance

DFS- disease-free survival, DSS- disease-specific survival, OS- overall survival, HR- hazard ratio, CI- confidence interval, CCI- Charlson comorbidity index, BMI- body mass index, PRETR ST- pretreatment clinical stage, RT- radiotherapy, LNY- lymph node yield, TRG- tumor regression grade, AL- anastomotic leakage, RT-S- time from completion of radiotherapy to surgery, Adj CT- adjuvant chemotherapy

	Univariate				Multivariate			
TRG 2–3	1.19	0.6477	2.187	0.5749				
No AL	Ref.							
AL	2.103	1.109	3.987	**0.0227**				
No AL	Ref.							
Early AL	1.292	0.5347	3.123	0.5691	1.415	0.5835	3.431	0.4425
Late AL	3.943	1.792	8.677	**< 0.001**	4.298	1.939	9.526	**< 0.001**
No adj CT	Ref.							
Adj CT	0.8261	0.2933	2.327	0.7177				
Bold values indicate statistical significance								
DFS- disease-free survival, DSS- disease-specific survival, OS- overall survival, HR- hazard ratio, CI- confidence interval, CCI- Charlson comorbidity index, BMI- body mass index, PRETR ST- pretreatment clinical stage, RT- radiotherapy, LNY- lymph node yield, TRG- tumor regression grade, AL- anastomotic leakage, RT-S- time from completion of radiotherapy to surgery, Adj CT- adjuvant chemotherapy								

Discussion

Despite the influence of ALs on long-term oncologic outcomes [2, 3], some reports did not confirm such a relationship [4, 14, 15]. To our knowledge, to date, no study has analyzed the significance of early and late ALs separately. There are several hypotheses explaining the possible mechanisms of AL-induced cancer relapse [16]. It was shown that during the resection procedure, exfoliated malignant cells which are present in the lumen of the colon have the potential to be implanted into the surrounding tissues. In the case of AL, these cells can penetrate beyond the lumen of the colon and initiate secondary tumor foci [17]. Another hypothesis highlights the role of acute phase factors and inflammatory mediators in tumor progression and metastasis. In vitro studies found that the peritoneal fluid collected from patients with ALs or from patients with other inflammatory processes in the abdominal cavity resulted in an increase in migration and invasion of cancer cell lines [18]. Additionally, both circulating cancer cells and immune cells show the tendency to migrate to inflammatory sites, thus enhancing the cascade of angiogenesis and proliferation. In light of the above theories, a long-term inflammatory process of low intensity which occurs in late ALs could explain their negative impact on survival as demonstrated by the authors of this study. Late ALs are an underestimated clinical problem in rectal cancer surgery. More than 50% of ALs may occur after hospital discharge, whereas 25%-40% may occur after 30 days following surgery [19, 20]. Definitions of late AL are different, depending on the authors. The common criterion is a period of over 30 days after surgery. However, a period of over 90 days and a less precise determination of AL after hospital discharge were also reported [19]. In accordance with the criterion we adopted, late ALs accounted for 40.5% of all ALs in our material. Late AL is more prevalent in patients with LI, which can be

explained by a delay in the diagnosis of AL. However, it was not confirmed in our material. The etiopathogenesis of late AL has not yet been elucidated. According to some reports, patient-dependent factors such as the severity of comorbidities or past RT, which may adversely affect the healing process, play a role in late ALs, as opposed to early ALs, where risk factors are mainly those that influence the course of surgery [20, 21] It was found that late ALs were more asymptomatic compared to early ALs. They were more prevalent in the form of fistulas and did not often require radical surgical intervention and became chronic over time. Chronic presacral sinus formation was more commonly found in late ALs (even in 65% of cases) [22]. The question arises whether the etiopathogenesis of early and late ALs is different, or whether all late ALs are in fact early ALs whose diagnosis was delayed in time. We are of the opinion that the results of our analysis may support the hypothesis of late ALs as early ALs that were diagnosed late with a long-term influence of the inflammatory factor.

We demonstrated a negative effect of CCI > 3 on DFS, DSS, and OS. The influence of comorbidities on the survival of cancer patients may result from several mechanisms. Comorbidities increase the risk of death during the follow-up for reasons other than cancer. They also limit the possibility of optimal treatment (e.g., adjuvant systemic treatment) and may also directly affect tumor progression. While the first two causes are evident and have an established impact on OS, the mechanism of the direct influence of comorbidities is still unclear, although the problem has been raised for a long time [23, 24]. Diabetes mellitus is the only disease in which a direct impact on DFS was confirmed in locally advanced and disseminated colorectal cancer, regardless of systemic treatment. A direct interaction between diabetes and the progression of colorectal cancer is associated with hyperinsulinemia, an increase in insulin-like growth factor, hyperglycemia, and inflammation [25]. Comorbidities may result in the exclusion of patients from adjuvant therapy. In our analysis, most patients did not require standard adjuvant therapy. Only 8.2% of patients underwent such therapy. However, we demonstrated the impact of CCI on DFS without the simultaneous influence of adjuvant chemotherapy on the probability of survival. Therefore, it seems that in ypN0 patients, the influence of CCI on DFS is the result of the direct influence of comorbidities on the course of cancer disease. However, the mechanism of this interaction remains unknown. Baretti *et al.* showed that the presence of comorbidities assessed by CCI had a significant negative impact on DFS and OS in stage II/III colorectal cancer patients. However, they did not perform the analysis of individual stages or locations. [11]. The influence of CCI on DFS and OS in patients with stages I-III colorectal cancer and different tumor location was demonstrated by Yamano *et al.* who did not find the influence of CCI on DFS in patients with stage II [26]. The mechanism by which CCI affects DSS can be complex and can be related to a direct influence of comorbidities on tumor progression.

In our analysis, we did not demonstrate the prognostic influence of LNY or its significance on understaging. LNY depends on several factors, including the response to neoadjuvant therapy, the method of surgery, and the technique and reliability of histological examination. Studies confirmed the effects of ionizing radiation on lymph nodes, including stromal atrophy and fibrosis, as well as lymphocyte count reduction [27, 28]. Preoperative radiotherapy was shown to reduce the total number of removed lymph nodes [5, 10]. Of note, studies found the reduction in the number of lymph nodes due to the response to neoadjuvant therapy associated with the response of the immune system. High levels of

CD8 + tumor infiltrating lymphocytes before treatment were associated with a good response to RCT and better DFS [29]. Studies on colon cancer patients found that despite the tendency to increase the number of removed nodes, the percentage of patients with metastatic lymph nodes did not increase [30, 31]. It was also shown that fat clearance increased the median number of retrieved lymph nodes in ypN0 rectal cancer patients from 12 to 19.5 compared to the conventional fixation method. However, it did not affect the long-term outcomes [32]. Thus, technical factors (both surgical and histological) seem to be of secondary importance in terms of understaging, particularly in centers experienced in colorectal surgery. Nevertheless, attempts are still made to determine the minimum number of lymph nodes to avoid understaging in the ypN0 group. The results of the studies are contradictory. It should be noted that most analyses reporting the cut-off point below which the understaging is found in ypN0 patients were based on single-center studies with a low (≤ 7) median number of removed lymph nodes in the entire group [33, 34] or were based on the data from the national multicenter registries. It does not offer the comparable quality of surgical treatment or the histological examination technique, and the mean LNY is the resultant of data from different centers [6, 7, 35]. In the case of analyses based on national registries, the same number of removed lymph nodes may be due to different causes, and thus the data may not be comparable [36]. Many studies indicated that LNY had no effect on understaging and thus on long-term survival in ypN0 patients. These included both single-center analyses [8, 9, 37] and two multicenter studies. One of them was based on data from 14 Italian high-volume referral centers, with the mean LNY of 12.9 [38], while the other was an American study which used the data from the California Cancer Registry and assessed DSS only [39]. Some research, including the above multicenter studies, reported total LNY without division into ypN0 and ypN + subgroups, which further complicates the inference because LNY may be significantly different in these subgroups [40]. The results of our analysis may indicate that LNY in ypN0 patients treated in reference centers should be considered in terms of the severity of the response to neoadjuvant therapy rather than as a determinant of the quality of surgical or histological procedures. Additionally, the problem of understaging may be not related to a single patient, but to a treatment center. In our material, the analysis of the survival curves showed no understaging. However, further studies are warranted to test this hypothesis. If it was confirmed, it would be essential to establish a minimum LNY for a given center, above which understaging is excluded.

Conclusions

Late AL and CCI > 3 are the factors that may influence long-term oncologic outcomes in ypN0M0 rectal cancer patients after neoadjuvant therapy and AR. No evidence of the impact of LNY on understaging was found.

List Of Abbreviations

AL- anastomotic leakage

AR- anterior rectal resection

CCI- Charlson comorbidity index

CRT- chemoradiotherapy

DFS- disease-free survival

DSS- disease-specific survival

HR- hazard ratio

IQR- interquartile range

LNY- lymph node yield

LVI- lymphovascular invasion

OS- overall survival

PNI- perineural invasion

RT- radiotherapy

SD- standard deviation

TRG- tumor regression grade

Declarations

Ethics approval and consent to participate

The study was approved by institutional ethics committee (KB/430-53/19)

Consent for publication

Not applicable

Availability of data and materials

All data generated or analysed during this study are included in this published article [and its supplementary information files].

Competing interests

The authors declare that they have no competing interests

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Author's contributions

MZ, MC and AC participated in the study conception and design, MZ, MC, WS, MS and PP participated in acquisition of the data, MZ, EC and AI participated in data analysis and interpretation, MZ has drafted the manuscript, AC substantively revised the manuscript.All authors read and approved the final manuscript.

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Figures

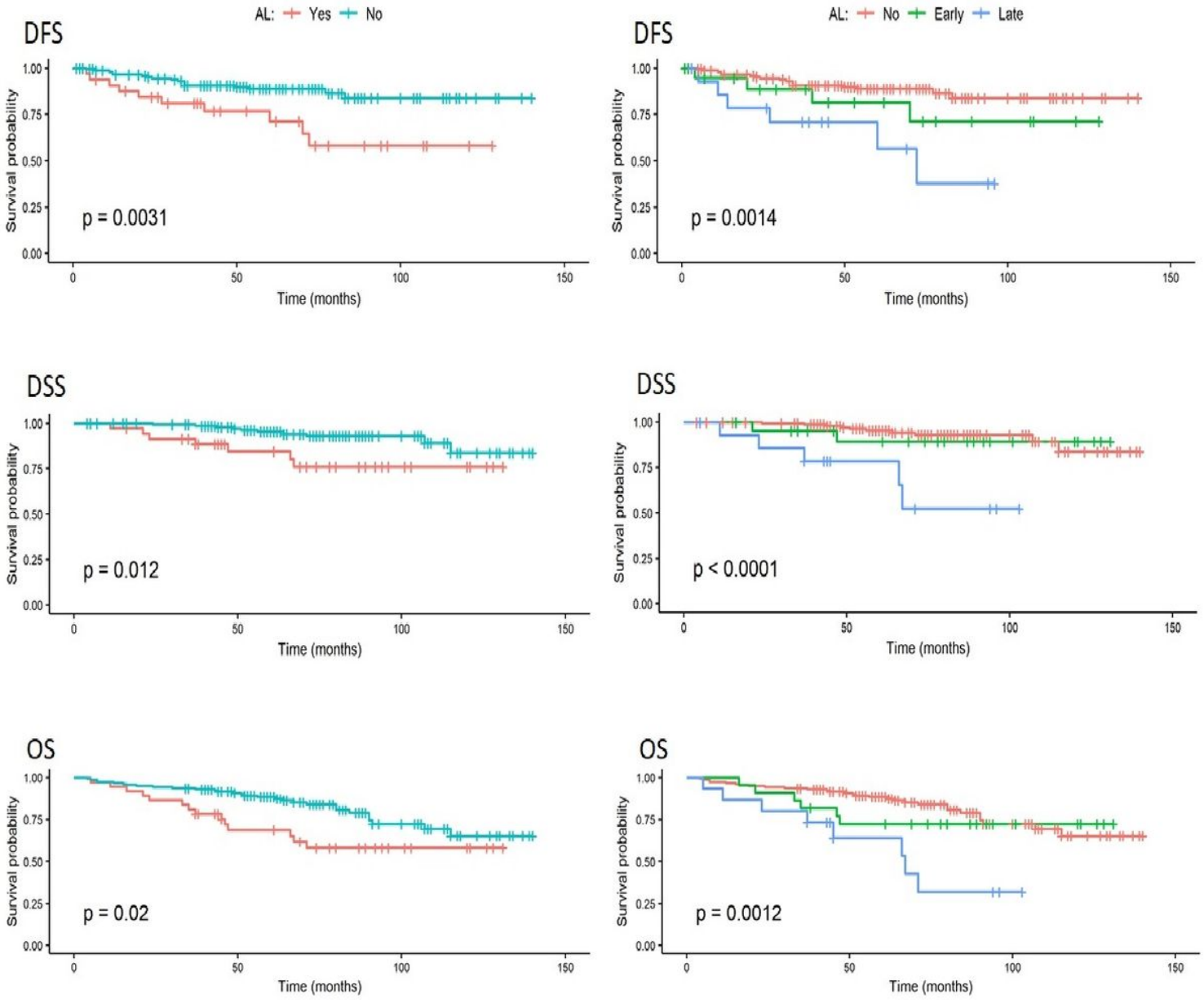

Figure 1

Survival analysis (DFS, DSS, and OS) of patients with ALs in the whole group and with the division into early and late ALs

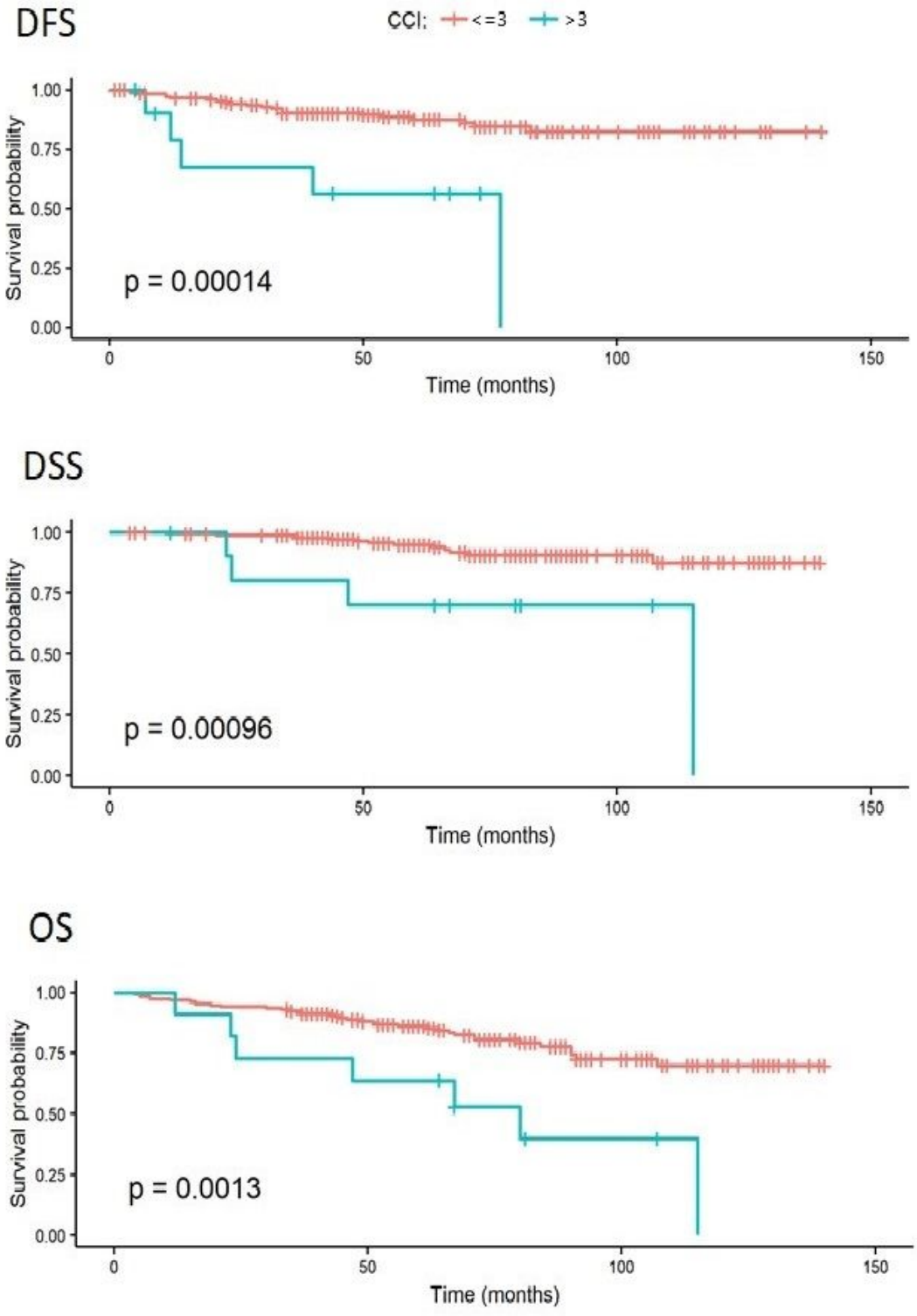

Figure 2

Survival analysis (DFS, DSS, and OS) depending on CCI (≤ 3 vs > 3)

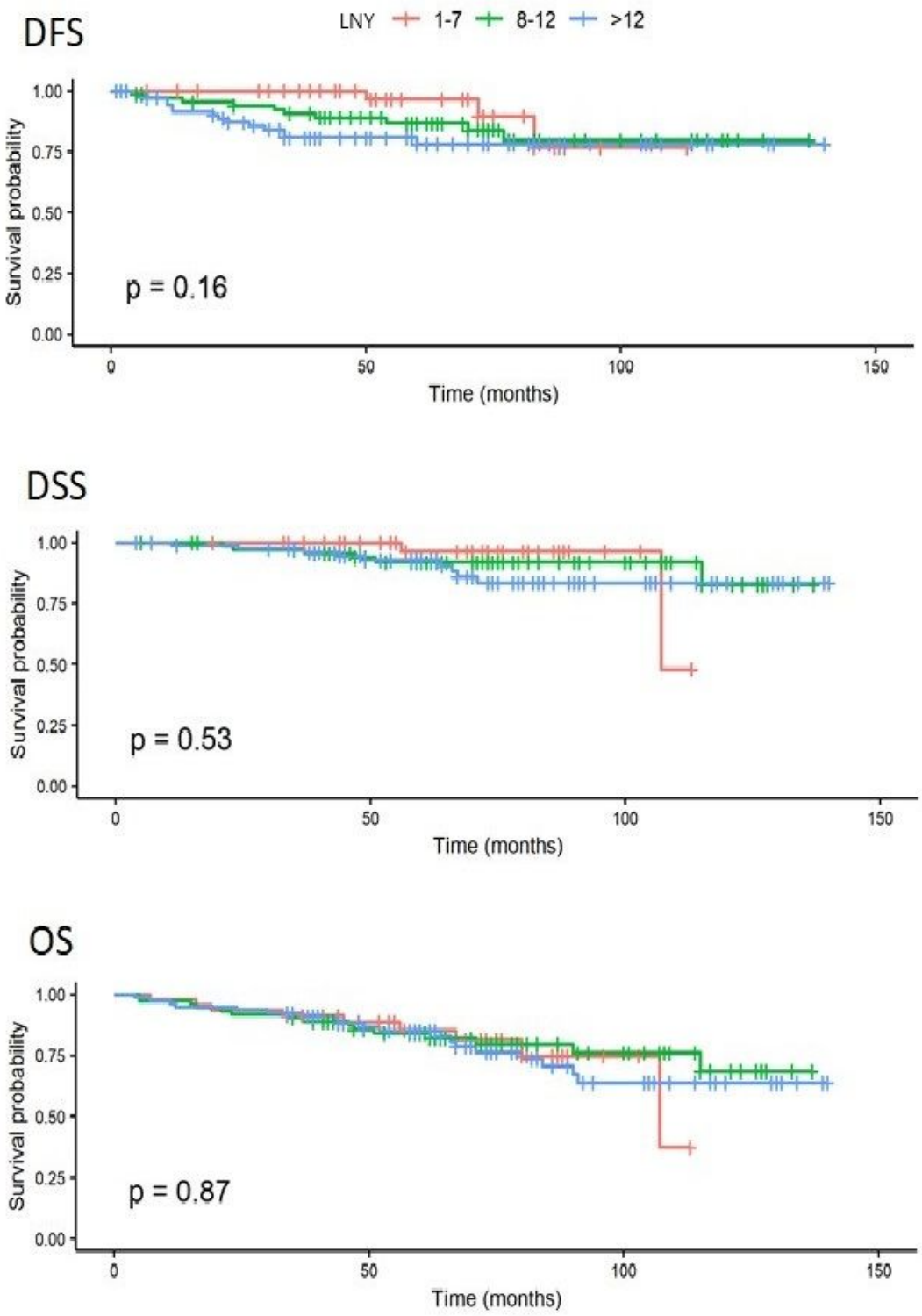

Figure 3

Survival analysis (DFS, DSS, and OS) of patients depending on LNY

Supplementary Files

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