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Negative impact of pretreatment anemia on local control after neoadjuvant chemoradiotherapy and surgery for rectal cancer

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Purpose: Although anemia is considered to be a contributor to intra-tumoral hypoxia and tumor resistance to ionizing radiation in cancer patients, the impact of pretreatment anemia on local control after neoadjuvant concurrent chemoradiotherapy (NACRT) and surgery for rectal cancer remains unclear.

Materials and Methods: We reviewed the records of 247 patients with locally advanced rectal cancer who were treated with NACRT followed by curative-intent surgery.

Results: The patients with anemia before NACRT (36.0%, 89/247) achieved less pathologic complete response (pCR) than those without anemia (p = 0.012). The patients with pretreatment anemia had worse 3-year local control than those without pretreatment anemia (86.0% vs. 95.7%, p = 0.005). Multivariate analysis showed that pretreatment anemia (p = 0.035), pathologic tumor and nodal stage (p = 0.020 and 0.032, respectively) were independently significant factors for local control.

Conclusion: Pretreatment anemia had negative impacts on pCR and local control among patients who underwent NACRT and surgery for rectal cancer. Strategies maintaining hemoglobin level within normal range could potentially be used to improve local control in rectal cancer patients.

Keywords: Anemia, Rectal cancer, Neoadjuvant therapy, Concurrent chemoradiotherapy

Introduction

Even though surgical resection is the primary treatment modality for rectal cancer, there is a high incidence of local recurrence after traditional surgery. Since Heald et al. [1] and Heald and Ryall [2] standardized a novel total mesorectal excision (TME) technique for rectal cancer; local failure has decreased from 30% to 10%. In addition, the development of a multidisciplinary team approach has allowed for the further improvement of local control, which has reported up to 2.4–5.6% according to clinical trials [3,4]. Despite these advanced management strategies for rectal cancer, local recurrence still

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remains a major obstacle to get cure from cancer as well as improved quality of life of patients.

Anemia is common condition in cancer patients and is suspected to contribute to intra-tumoral hypoxia, which can attribute to radio-resistance. Previous studies have also revealed that low hemoglobin (Hb) level before or during radiotherapy is an adverse factor for local disease control and patient survival [5]. In addition, a number of studies have shown that anemia is an independent predictive factor for dismal overall survival rates and poor local control at various tumor sites, including head and neck cancer [6,7], lung cancer [8,9], cervical cancer [5], and esophageal cancer [10,11].

However, it is still unclear whether a low Hb level is an adverse factor for local control and survival in patients undergoing neoadjuvant concurrent chemoradiotherapy (NACRT) for locally advanced rectal cancer. In the present study, it was predicted that anemia would represent a major factor influencing the outcome in rectal cancer patients, and here we report the results of this study with an emphasis on the effect of anemia on local control.

Materials and Methods

1. Patient selection

A total of 301 rectal cancer patients were treated with NACRT at Samsung Medical Center between March 2002 and December 2007. Eligibility criteria were as follows: 1) histologically proven, clinical stage II (T3-4 without lymph node metastasis) or III (any T with lymph node involvement) adenocarcinoma of the rectum; 2) absence of distant metastasis at diagnosis; 3) no serious medical condition at diagnosis; 4) no history of previous or any other current malignancies; 5) no history of previous chemotherapy or radiotherapy; and 6) receipt of curative-intent treatment for rectal cancer. Consequently, 247 patients were included in the final analysis.

Hb data were collected from patient medical records. All blood data, which was obtained either just before or at the beginning of radiotherapy, was examined in each patient. Anemia was defined as Hb level of ≤12.0 g/dL in female and ≤13.5 g/dL in male patients according to data from the Third National Health and Nutrition Examination Survey (NHANES III) [12].

2. Treatment modality

Preoperative radiotherapy was delivered to the whole pelvis with a dose of 45 Gy in 25 fractions or 44 Gy in 22 fractions. The radiation field encompassed a volume that included the gross tumor, mesorectum, presacral space, and the regional perirectal, internal iliac, presacral, and distal common iliac lymphatics. Preoperative chemotherapy was delivered concurrently with radiotherapy based on 5-fluorouracil or capecitabine regimens.

All patients received radical surgery 6 to 8 weeks after NACRT completion. Of the 247 patients included in the study, 225 (91.1%) patients received adjuvant chemotherapy.

3. Statistical analysis

Univariate and multivariate analyses were performed using logistic regression analysis to identify the factors associated with pathologic complete response (pCR). Variables with $p < 0.1$ on univariate analysis and general variables such as age, gender were entered into multiple logistic regression model. Rates of local control, disease-free survival, and overall survival were estimated by the Kaplan-Meier method. Comparisons of survival distributions were performed using the log-rank test. Multivariate analysis with Cox proportional hazard model was used to determine the independent predictive factors significantly impacting survival including clinical and pathologic findings. Statistical analysis was performed using SPSS ver. 18.0 (SPSS, Chicago, IL, USA).

4. Ethics statement

This study was approved and exempted of permission by the Institutional Review Board of Samsung Medical Center, Sungkyunkwan University (IRB no. 2011-04-084).

Results

1. Patient characteristics

Patient and tumor characteristics at baseline are listed in Table 1. There was no significant difference between the anemic and non-anemic patients, except that there was a tendency of anemic patients having more advanced disease at diagnosis. The median follow-up period was 44.0 months (ranges, 8.0 to 100.0 months). The median age was 55 years (range, 25 to 76 years), and a total of 53 (21.5%) and 194 (78.5%) patients were diagnosed with clinical stage II (lymph node negative) and stage III (lymph node positive) disease, respectively. About half of the patients received concurrent chemotherapy based on 5-fluorouracil (48.6%) and the other half received capecitabine (51.4%). The majority of patients (76.5%) underwent low

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Table 1. Characteristics of patients and tumors

Characteristic	All patients (n = 247)	Patients without anemia (n = 158)	Patients with anemia (n = 89)	p-value[c]
Age (yr)				0.408
≤60	161 (65.2)	106	55	
>60	86 (34.8)	52	34	
Gender				0.779
Male	166 (67.2)	105	61	
Female	81 (32.8)	53	28	
Distance from anal verge (cm)				0.572
≤5	169 (68.4)	106	63	
>5	78 (31.6)	52	26	
Initial CEA level (ng/mL)				0.351
≤5	189 (76.5)	124	65	
>5	58 (23.5)	34	24	
Anemia before NACRT				
Yes	89 (36.0)	-	-	
No	158 (64.0)	-	-	
Concurrent chemotherapy				0.602
5-Fluorouracil	120 (48.6)	75	45	
Capecitabine	124 (50.2)	80	44	
Capecitabine + oxaliplatin	3 (1.2)	3	0	
Clinical T stage				0.016
cT2	8 (3.2)	4	4	
cT3	214 (86.7)	144	70	
cT4	25 (10.1)	10	15	
Clinical N stage				0.054
cN0	53 (21.5)	40	13	
cN+	194 (78.5)	118	76	
Type of surgery				0.051
Sphincter-preserving surgery[a]	203 (82.2)	131	64	
APR[b]	44 (17.8)	27	25	
Circumferential resection margin				
Positive	13 (5.3)	8	5	
Negative	234 (94.7)	150	84	
Post-CRT pathologic T stage				0.142
ypT0	46 (18.6)	36	10	
ypTis	4 (1.6)	4	0	
ypT1	10 (4.0)	7	3	
ypT2	64 (25.9)	38	26	
ypT3	115 (46.7)	68	47	
ypT4	8 (3.2)	5	3	
Post-CRT pathologic N stage				0.818
ypN0	177 (71.7)	114	63	
ypN1	51 (20.6)	31	20	
ypN2	19 (7.7)	13	6	
Post-CRT M stage				0.715
ypM0	239 (96.8)	152	87	
ypM1	8 (3.2)	6	2	

Table 1. Continued

Characteristic	All patients (n = 247)	Patients without anemia (n = 158)	Patients with anemia (n = 89)	p-value[c]
Tumor downstaging				0.690
Yes	133 (53.8)	87	46	
No	114 (46.2)	71	43	
Node downstaging				0.291
Yes	133 (53.8)	81	52	
No	114 (46.2)	77	37	

CEA, carcinoembryonic antigen; NACRT, neoadjuvant concurrent chemoradiotherapy; APR, abdominoperineal resection; CRT, concurrent chemoradiotherapy.
[a]Included six cases of local excision and eight Hartmann's operation. [b]Included one case of pelvic exenteration. [c]Chi-square test.

Table 2. Results of univariate and multivariate analysis on pretreatment characteristics predicting pathologic complete response

Variable	Univariate analysis			Multivariate analysis		
	OR	95% CI	p-value	OR	95% CI	p-value
Age (yr)						
≤60 vs. >60	0.811	0.397-1.655	0.564	-	-	-
Gender						
Male vs. Female	0.425	0.187-0.967	0.041	0.409	0.178-0.937	0.035
Distance from anal verge (cm)						
≤5 vs. >5	0.842	0.406-1.749	0.646	-	-	-
Initial CEA level (ng/mL)						
≤5 vs. >5	0.729	0.317-1.679	0.458	-	-	-
Anemia before NACRT						
No vs. Yes	0.360	0.159-0.817	0.015	0.348	0.153-0.796	0.012
Clinical T stage						
cT2-3 vs. cT4	0.640	0.182-2.244	0.486	-	-	-
Clinical N stage						
cN0 vs. cN+	0.625	0.295-1.326	0.220	-	-	-

CEA, carcinoembryonic antigen; NACRT, neoadjuvant concurrent chemoradiotherapy; OR, odds ratio; CI, confidence interval.

anterior resection (LAR) of the rectum.

The median pretreatment Hb level was 13.5 g/dL (range, 7.0 to 17.7 g/dL). Among the 247 patients, 89 (36.0%) patients had anemia before treatment. In the present study, Hb level was corrected in 10 patients with levels less than 8.0 to 9.0 g/dL according to institutional policy; however, all patients remained anemic during radiotherapy.

Eight patients developed distant metastasis to the liver after NACRT. All these patients received resection of the primary and metastasectomy or radiofrequency ablation of the metastatic tumors. Complete resection was performed in 234 patients; 13 (5.3%) patients had a positive circumferential resection margin (CRM).

2. Tumor response and anemia

Pathological tumor staging was ypT0 in 46 (18.6%), ypTis in 4 (1.6%), ypT1 in 10 (4.0%), ypT2 in 64 (25.9%), ypT3 in 115 (46.6%), and ypT4 in 8 (3.2%) patients. Tumor downstaging and nodal downstaging was achieved in 133 (23.8%) patients, respectively (Table 1). Complete response was achieved in 42 (17.0%) patients based on pathologic examination. Predictors of pCR on univariate analysis were found to be female gender (p = 0.041) and anemia before treatment (p = 0.015) (Table 2). Multivariate analysis showed that pretreatment anemia remained significant factor for predicting pCR after NACRT (p = 0.012) (Table 2).

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Table 3. Results of univariate and multivariate analyses of factors affecting local control

Variable	Univariate		Multivariate		
	LC at 3 yr (%)	p-value	Hazard ratio	95% CI	p-value
Age (yr)					
≤60 vs. >60	91.1/94.6	0.311	0.564	0.181-1.762	0.325
Gender					
Female vs. Male	92.1/92.9	0.546	1.059	0.397-2.824	0.909
Distance from anal verge (cm)					
≤5 vs. >5	92.4/91.8	0.908	-	-	-
Initial CEA level (ng/mL)					
≤5 vs. >5	91.7/94.1	0.508	-	-	-
Anemia before NACRT					
No vs. Yes	95.7/86.0	0.005	2.952	1.076-8.094	0.035
Clinical T stage					
cT2-3 vs. cT4	93.4/80.7	0.028	1.780	0.560-5.655	0.329
Clinical N stage					
cN0 vs. cN+	95.9/91.2	0.544	-	-	-
Circumferential resection margin					
Negative vs. Positive	92.7/84.6	0.246	-	-	-
Post-CRT pathologic T stage					
ypT0-2 vs. ypT3-4	99.2/84.8	<0.001	6.005	1.328-27.143	0.020
Post-CRT pathologic N stage					
ypN0 vs. ypN+	96.4/80.8	0.001	2.881	1.093-7.598	0.032

LC, local control; CEA, carcinoembryonic antigen; CI, confidence interval; NACRT, neoadjuvant concurrent chemoradiotherapy.

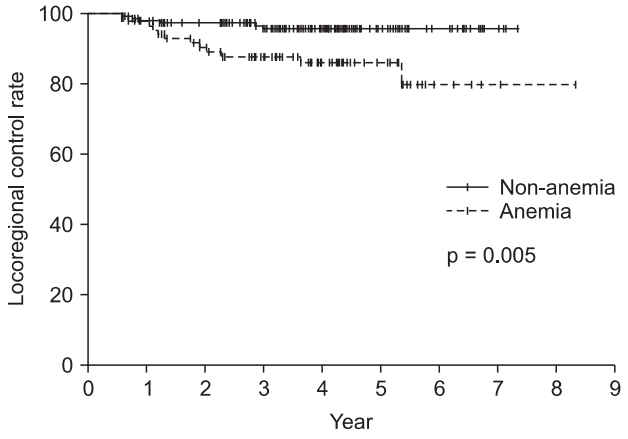

Fig. 1. Local control rate in patients with pretreatment anemia vs. non-anemic patients.

3. Univariate and multivariate survival analysis of clinico-pathologic variables associated with local control

Three- and five-year overall survival (OS) rate was 90.1% and 81.1%, respectively. Disease-free survival (DFS), distant metastasis-free survival (DMFS) and local control rate at three years were 77.8%, 80.1%, and 92.9%, respectively.

Improved local control was significantly associated with clinical tumor stage (p = 0.028), pathologic tumor stage (p < 0.001), and pathologic node stage (p = 0.001) on univariate survival analysis (Table 3). Although positive CRM was not significantly associated with local control (p = 0.246), a trend towards decreased overall survival was observed (p = 0.075). The presence of anemia before radiotherapy was significantly associated with reduced probability of local control based on univariate survival analysis (p = 0.005) (Fig. 1), although no significant differences in DMFS, DFS, or OS were observed on the basis of Hb level.

In multivariate analysis, the Cox proportional analysis showed that anemia had a significant adverse effect on local control after NACRT and surgery for rectal cancer (hazard ratio, 2.95; 95% confidence interval, 1.076 to 8.094; p = 0.035) (Table 3).

Discussion and Conclusion

Anemia is frequently present in patients during the course of cancer. It may be a presenting sign of malignancy or a consequence of anticancer therapy. Harrison et al. reported that anemia, when defined at Hb level of <2.0 g/dL, is relatively common in patients presenting for radiotherapy with an estimated incidence of up to 40–60% [13]. During radiotherapy, the prevalence of anemia increases to up to

80% depending on tumor type [13]. As locally advanced rectal cancers may benefit from a combination of chemotherapy and radiotherapy, anemia may represent an important factor hindering favorable clinical outcomes.

Numerous studies have found anemia to be a predictor of poor local control and survival at various sites of malignancy including rectal cancer. Box et al. [14] demonstrated that non-anemic patients achieved better tumor response and less local recurrence (7% vs. 38%, p = 0.003) and improved OS (91% vs. 61%, p = 0.021) than anemic patients. Berardi et al. [15] also showed that DFS was worse in patients with Hb ≤12.0 g/dL compared to those with Hb >12.0 g/dL (p = 0.018). Rades et al. [16] found that locally recurrent rectal cancer patients with Hb levels ≥12.0 g/dL had significantly better local control than those with levels <12.0 g/dL (p < 0.001). Hb levels ≥12.0 g/dL were also associated with significantly better survival in their study (p = 0.031). Our results were consistent with these studies showing that pretreatment anemia could affect the clinical outcome in Korean patients as well. Although Lee et al. [17] also investigated the predictive role of anemia in Korean patients treated with NACRT, in that they focused on whether anemia influences the pathologic response, our results showed further that it could be one of prognostic factor affecting local control.

The most important prognostic factor affecting local control and survival is tumor extent, which is commonly evaluated based on the Tumor-Node-Metastasis staging system. Our data also confirmed that pathologic tumor and nodal stages influenced local control, DFS, and OS (ypT: p < 0.001 for local control, p < 0.001 for DFS, p = 0.006 for OS; ypN: p = 0.001 for local control, p < 0.001 for DFS, p = 0.001 for OS). However, the influence of Hb level was only for local control in our study presenting no significant differences in DFS and OS between anemic and non-anemic patients (3-year DFS: 75.7% vs. 79.0%, p = 0.355; 3-year OS: 89.0% vs. 90.7%, p = 0.767). It seems that higher local control in non-anemic patients does not directly translate into improved OS because the majority of failure patterns were distant metastases (51 of 247 patients, 20.6%) rather than local recurrences (18 of 247 patients, 7.3%).

Besides the negative impact on response to radiotherapy, anemia itself is also an important factor to be considered during treatments. Since anemia is a major cause of fatigue, and fatigue is the most common symptom in cancer patients resulting in decreased quality of life, recognizing and correcting anemia is important for quality of life improvement in cancer patients [18-20]. In most clinical settings, severe anemia is treated with red blood cell transfusions, but mild-to-moderate anemia has been usually neglected. However, the early correction of anemia up to an Hb level of 12.0 to 14.0 g/dL may improve both local control as well as quality of life.

There are numerous methods to correct anemia, including iron supplements, transfusion of packed red blood cells, and/or the administration of erythropoietin-stimulating agents (ESAs). ESAs were initially used to treat anemia in patients with chronic renal failure, including those on hemodialysis. Recent clinical trials have established that ESAs are also effective in raising Hb levels, decreasing the need for transfusions and subsequently improving quality of life in patients with cancer-related and chemotherapy-induced anemia [18,21,22]. While there is general agreement that ESAs are not indicated in anemic cancer patients who are not receiving chemotherapy [22], the use of ESAs in patients receiving radiotherapy remains controversial. Although the effectiveness of ESAs on survival was not demonstrated by a recent randomized clinical trial for head and neck cancer patients undergoing radiotherapy [23,24], our data suggest that similar trials might be needed for rectal cancer patients.

In conclusion, we propose that pretreatment anemia represents an independently predictive factor for local control in patients with rectal cancer undergoing NACRT and surgery and exerts an adverse effect on treatment results. A prospective validation of Hb level as a predictive factor is mandatory.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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