Immediate postoperative intraperitoneal drain CEA level can aid in recurrence prediction in rectal cancer

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ABSTRACT

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Colorectal cancer (CRC) remains a leading cause of cancer-related mortality globally, with distant metastasis contributing significantly to poor outcomes post-surgery. Current diagnostic markers, such as carcinoembryonic antigen (CEA), lack sufficient sensitivity and specificity when used alone. This study investigates the potential of CEA levels in postoperative drainage fluid as a prognostic indicator for CRC recurrence.

A retrospective analysis was conducted on 319 patients who underwent curative resection for CRC between July 2014 and November 2018. Patient demographics, perioperative outcomes, and CEA levels in serum and drainage fluid were analyzed. Recurrence-free survival (RFS) was assessed based on CEA levels.

Elevated CEA levels in postoperative drainage fluid within the first day correlated significantly with increased recurrence risk (OR 3.10, 95% CI 1.54-6.24, p=0.002). Lymph node metastasis and minimally invasive surgery were also independent risk factors for recurrence. Rectal cancer patients showed a stronger association between elevated postoperative CEA and recurrence compared to colon cancer patients.

Monitoring postoperative CEA levels, particularly in rectal cancer patients, may aid in identifying those at higher risk of recurrence, warranting closer surveillance. Comparison of different patterns of CEA elevation over time revealed varying recurrence rates, emphasizing the potential utility of serial CEA measurements.

Elevated CEA levels in postoperative drainage fluid, especially within the first day, are associated with increased recurrence risk in CRC patients. Incorporating postoperative CEA monitoring into surveillance strategies may enhance recurrence detection and patient management, particularly in rectal cancer cases. Further research is needed to validate findings and establish optimal cutoff values for clinical use.

Key words : colorectal neoplasms, carcinoembryonic antigen, postoperative period, ascitic fluid

1. Introduction

Colorectal cancer continues to be one of the top leading causes of cancer-related deaths worldwide[1]. In most cases, distant metastasis is the main culprit behind patients' morbidity and mortality after curative resection. It is imperative to develop effective diagnostic and prognostic markers to detect disease progression more accurately and promptly. In that context, there has been growing interest in studying the role of various tumor markers in colorectal cancer. One such marker of interest is carcinoembryonic antigen[2].

Carcinoembryonic antigen (CEA) is a glycoprotein that is normally produced during fetal development but can also be expressed in excessive amounts by certain tumor cells, including those in colorectal cancer. Currently in colorectal malignancies, CEA level of peripheral blood sample is checked at the time of diagnosis and during follow up after curative resection. Current guideline for surveillance after curative resection, according to NCCN guidelines recommends checking CEA level every 3-6 months for the first two years and every 6-12 months for the following 3 years along with other imaging studies and physical examination[3].

However, the role of CEA in surveillance after curative resection has been secondary to other work up such as imaging studies and physical examination due to its limited sensitivity and specificity when used individually. Moreover, CEA levels can be influenced by various factors such as inflammation, liver diseases, and non-colorectal malignancies, raising caution in interpretation of the results.[4] To overcome these limitations, researchers have started exploring alternative sources for CEA measurement in colorectal cancer patients.

One potential source for CEA measurement in colorectal cancer patients is ascites. CEA level of ascites or intraperitoneal fluid has been explored in several studies previously, but many of them focused on its diagnostic value in detecting peritoneal metastasis[5]. Also, most of previous studies examined CEA level measured before the curative resection of colorectal cancer in ascites aspirate or intraperitoneal lavage fluid intraoperatively. However, there is limited research on the CEA level in intraperitoneal drainage fluid postoperatively and its potential as a prognostic indicator for colorectal cancer.

To address this gap in the literature, the objective of this research is to evaluate the CEA level

measured in postoperative drainage fluid of patients with colorectal cancer and its role and efficacy as a prognostic factor.

2. Materials and Methods

2.1 Patient selection

Using a prospectively maintained database of consecutive cases at a single tertiary medical center in Korea, patients who underwent surgery for colorectal malignancies between July of 2014 and November of 2018 were screened and reviewed retrospectively. All patients over the age of 18 who underwent curative resection for colorectal cancer and had postoperative drainage tubes available for analysis were included in the study. Patients who had palliative resection only, those without any bowel resection, intraperitoneal drainage placed, stage IV disease, emergency cases, inflammatory bowel disease-related cases, or those with incomplete data were excluded from the study. Electronic medical records were used to review patients' baseline characteristics, operative outcomes, and pathologic outcomes.

2.2 Surgical procedures

All patients were admitted one day before scheduled surgery and discharged on the day of or one day after soft diet was resumed. Perioperative management was done according to ERAS (enhanced recovery after surgery) protocols. For colon cancer, surgical resection and lymph node dissection were done under central vessel ligation and complete mesocolic resection principles. Intracorporeal or extracorporeal anastomosis was chosen for each case accordingly. For rectal cancer, oncologic principles were followed and total mesorectal resection or tumor-specific mesorectal resection was chosen depending on tumor height. At the end of each surgery, intraperitoneal drainage tubes were placed through one of the working ports used for laparoscopic or robotic instrument access, or at either lower side of abdomen for open laparotomy cases. Tips of drainage tubes were placed in pelvic cavity, but for two-armed tubes, upper arm could be placed along paracolic gutter of inserted side.

2.3 Carcinoembryonic antigen

All patients were planned and executed according to standard treatment protocol perioperatively, and postoperative follow-up outpatient clinic visits were also done per standards. For every patient, carcinoembryonic antigen level in serum sample (sCEA) was tested at the time of diagnosis, within one month before surgical resection, and after 1 week of surgery. As for the CEA levels in the postoperative drainage fluid (pCEA), it was measured using the same radioimmunologic assay for serum samples at immediate postoperative day (POD0), postoperative day 1(POD1) and 5 (POD5), on which day the drain tubes were usually removed. CEA level was considered 'elevated' when it was measured greater than 5ng/mL both in serum and in intraperitoneal drain samples. The results of CEA levels were analyzed for association with other clinicopathological characteristics.

2.4 Outcomes

Our primary outcome was recurrence-free survival between within normal limits pCEA level and elevated pCEA level. Secondary outcomes include perioperative outcomes such as postoperative complications, pathologic results, and oncologic outcomes.

2.5 Statistical analysis

Descriptive statistics were shown in number and percentage, mean with standard deviation, and median with interquartile range. Analysis of association was done using the Chi-square test or Fisher's exact test, with p value of <0.05 being considered as statistically significant. Overall follow-up period was measured from the time of surgery to the date of the last visit to the hospital or recorded death, whichever came first, in months. Event for recurrence-free survival was defined as any (local/regional/systemic) recurrence of colorectal cancer or cancer-related death. Univariate analysis was done using the log-rank test, and multivariable Cox proportional hazards regression modeling was used to calculate hazard ratios for recurrence risk. parameters with a p value less than 0.05 were used in multivariate analysis. Statistical analyses were performed using SPSS v.26.0 (IBM).

3. Results

3.1 Patient characteristics

Between 2014 July and 2018 November, there were 529 operations conducted for colon or rectal cancer. 180 cases were excluded if there weren't bowel resection and anastomosis, intraperitoneal drainage tube placement, pathologic report showing stage IV disease or something other than colorectal primary cancer. Total of 319 patients were included for analysis.

Median age for the entire cohort was 62 years old (interquartile range, IQR, 54-72), and there were 185 (58.0%) male patients and 134 (42.0%) female patients. Mean body mass index (BMI) was 23.3 (standard deviation, SD 0.19). there were 200 cases (62.7%) of colon cancer, and 119 (37.3%) of rectal cancer. Most of rectal cancer patients (96/119 80.7%) had neoadjuvant chemoradiation. Most of surgeries were done in minimally invasive methods, 207 laparoscopic cases (64.9%), and 98 robotic cases (30.7%), and 14 cases (4.4%) were done under laparotomy. Patients' basic characteristics are shown in Table 1.

Table 1. Patients' baseline characteristics

	N (%), median (IQR)
Male	185 (58.0)
Female	134 (42.0)
Age	62 (54-72)
BMI	23.3 (0.19)
ASA class	
I	32 (10.0)
II	161 (50.5)
III	118 (37.0)
IV	8 (2.5)
Operation method	
Open	14 (4.4)
Laparoscopic	207 (64.9)
Robotic	98 (30.7)
†Conversion	8 (2.6)
Colon	200 (62.7)
Rectum	119 (37.3)
Preop CRT	96 (80.7)

BMI: body mass index, ASA: American society of anesthesiologist, CRT: chemoradiotherapy, AJCC: American Joint Committee on Cancer, pCR: pathologic complete remission.

† conversion: all conversion cases were observed in laparoscopic cases

3.2 Perioperative outcomes

Median operative time was 240 minutes (IQR 189-300 minutes) and median amount of estimated blood loss was 50mL (IQR 20-100mL). Conversion to laparotomy was needed in eight (8/207, 3.9%) laparoscopic cases, and none in robotic cases.

On pathologic report, there were 21(6.6%) cases showing complete remission, 86 (27.0%) of stage 1, 94(29.5%) of stage 2, and 118 (37.0%) of stage 3. Median number of retrieved lymph nodes were 19 (IQR 13-28), and those positive for metastasis was 0 (IQR 0-1. Median length of proximal resection margin was 10.0cm (range 7.0-15.0cm), and it was 5.0cm (IQR 3.0-10.0cm) for distal margin. Median tumor size at maximal diameter was 3.0cm (IQR 2.0-5.0cm). Median duration of hospital stay was 7days (IQR 6-9days). There were 25 (7.8%) patients who had postoperative complications that were grade 2 or higher under Clavien-Dindo classification. (Table 2)

Table 2. Operative and pathologic findings

	N (%), median (IQR)
Preoperative symptoms†	13 (4.1)
Operation time (min)	240 (189-300)
Estimated blood loss (mL)	50 (20-100)
Pathologic stage (AJCC)	
pCR	21 (6.6)
1	86 (27.0)
2	94 (29.5)
3	118 (37.0)
Lymph node, number	
Harvested	19 (13-28)
Metastatic	0 (0-1)
Resection margin, length(cm)	
Proximal	10.0 (7.0-15.0)
Distal	5.0 (3.0-10.0)
Tumor size (cm)	3.0 (2.0-5.0)
Total hospital stay (days)	7 (6-9)
Postoperative complications	25 (7.8)

† preoperative symptoms: obstructive symptoms requiring stent insertion, gastrointestinal bleeding

3.3 CEA level results

Levels of carcinoembryonic antigen (CEA) are shown on table 3. Median level found in peripheral blood sample preoperatively (sCEA) was 2.48ng/dL (IQR 1.47-5.08ng/dL), and 80 (25.1%) patients had elevated sCEA. For sCEA checked postoperatively, median level was 1.25ng/mL (IQR 0.85-2.08ng/dL), and 6 (1.9%) patients had elevation. For samples taken from intraperitoneal drainage tubes, median level at POD 0, 1, and 5 were 6.86ng/dL (IQR 3.07-19.99ng/dL), 1.23ng/dL (IQR 2.22-10.36ng/dL), and 2.04 (1.14-5.30ng/dL) respectively. Patients who had elevated level at each sampled day were 173 (54.2%), 140 (43.9%), and 60 (18.8%) on POD0, 1, and 5 respectively.

Table 3. Carcinoembryonic antigen levels in different samples and patients with elevated measurements

		Median (IQR)	**No. of patients with elevated [CEA], N(%)**
[CEA] (ng/dL) from peripheral blood			
	preop	2.48 (1.47-5.08)	80 (25.1)
	postop 1week	1.25 (0.85-2.08)	6 (1.9)
[CEA] (ng/dL) from peritoneal drainage			
	POD 0	6.86 (3.07-19.99)	173 (54.2)
	POD 1	4.23 (2.22-10.36)	140 (43.9)
	POD 5	2.04 (1.14-5.30)	60 (18.8)

IQR: interquartile range, CEA: carcinoembryonic antigen, POD: postoperative day

3.4 Disease recurrence

Table 4. Univariate and multivariate regression model for recurrence risk

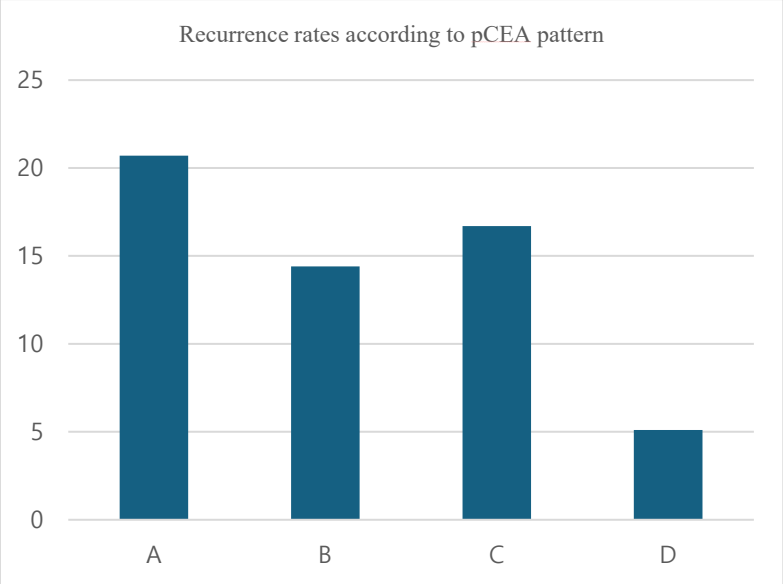
	univariate			multivariate		
	OR	95%CI	P	HR	95%CI	P
Age > 50	1.28	0.58-2.86	0.542			
Male	0.87	0.44-1.70	0.679			
MIS op	0.24	0.08-0.76	**0.015**	0.16	0.04-0.63	**0.008**
Tumor size≥3cm	0.85	0.43-1.70	0.653			
Rectal cancer	1.37	0.71-2.66	0.351			
pT≥3	2.82	1.30-6.13	**0.009**	1.07	0.43-2.64	0.695
Node metastasis	5.13	2.50-10.53	**<0.001**	3.79	1.76-8.18	**0.001**
***Pre-op complication**	2.12	0.56-8.03	0.271			
Pre-sCEA ▲	1.67	0.83-3.36	0.154			
POD7-sCEA ▲	1.37	0.16-11.98	0.779			
pCEA POD 0 ▲	3.14	1.32-7.43	**0.009**	2.01	0.68-5.94	0.188
pCEA POD 1 ▲	3.10	1.54-6.24	**0.002**	2.70	1.23-5.92	**0.013**
pCEA POD 5 ▲	1.77	0.79-3.98	0.166			

For a median follow up of 56 months, there were 41 (12.9%) cases of recurrences. We compared recurrence rates between groups with within normal limits (WNL) and elevated CEA levels in preoperative serum sample, postoperative intraperitoneal samples at POD 0,1, and 5 first to overview any possible trends. For preoperative sCEA, there were 14 (17.5%) recurrences for those with elevated sCEA compared to 27 (11.3%) for those with WNL sCEA (*p=0.177*). For postoperative pCEA, there was statistically significant difference in recurrence rates between elevated level vs. WNL level checked at POD 0 and 1 (pCEA POD0 29 (16.8%) vs. 7 (6.0%), *p=0.003*; POD1 28 (20.0%) vs. 13 (7.5%), *p=0.001*).

On univariate analysis for recurrence risk of potential factors, as shown in table 4, conducting surgery under minimally invasive methods (OR 0.24 95%CI 0.08-0.76, p=0.015), pathologic T stage 3 or higher (OR 2.82 95%CI 1.30-6.13, p=0.009), lymph node metastasis (OR 5.13 95%CI 2.50-10.53, p<0.001), and elevated pCEA levels at POD 0 (OR 3.14 95%CI 1.32-7.43, p=0.009) and 1 (OR 3.10 95%CI 1.54-6.24, p=0.002) had statistically significant relations to recurrence risk. Using aforementioned factors for multivariate analysis, results showed lymph node metastasis (OR 3.79 95%CI 1.76-8.18, *p=0.001*) and elevated pCEA level at POD 1 (OR 2.70 95%CI 1.23-5.92, *p=0.013*) were independent risk factors for recurrence, and performing MIS was a factor that lowered risk for recurrence (OR 0.16 95%CI 0.04-0.63, *p=0.008*). On subgroup analysis between colon and rectal cancer patients, similar trends were seen except for a few differences. In colon cancer cohort, only node metastasis was a statistically significant independent risk factor for recurrence (OR 6.19 95%CI 2019-17.46, p=0.001). Elevated pCEA at POD1 did not reach statistical significance after multivariate adjustment, but still showed trends toward raising risk of recurrence (OR 1.76 95%CI 0.67-4.62, p=0.111). Rectal cancer cohort on the other hand, showed nodal metastasis (OR 4.99 95%CI 1.46-17.08, p=0.011) and elevated pCEA at POD 0 (OR 7.82 95%CI 1.54-39.55, p=0.013) to be independent risk factors for recurrence, and MIS operation (OR 0.04 95%CI 0.01-0.46, p=0.010) to be a factor to reduce the risk. (Appendix 3-4)

Since levels of pCEA were checked over the course of patients' postoperative periods, we were able to analyze recurrence rates between four different patterns of pCEA level flows (Figure 1); those who had elevated pCEA within 1 day of operation and still showed elevation at POD 5 (A) , those who had elevation then drop to normal limits (B), those who did not show elevation but had increased level at the end (C), and finally those who never had pCEA elevation throughout the postoperative period (D). Recurrence rates differed between the groups significantly, with highest to lowest rates shown in pattern A, C, B, and D respectively (A 20.7%, C 16.7%, B 14.4%, and D 5.1%, p=0.010). Furthermore, patients with elevated pCEA at any time period but did not have sCEA elevation preoperatively were at higher risk of recurrence than those that did not show pCEA elevation, but this difference did not reach statistical significance (22/130 16.9% vs. 19/189 10.1%, p=0.088).

Figure 1. Recurrence rate differences according to pCEA change pattern



	pCEA level				*P*
	Immediate postop	POD 5	Pt. No (%)	Recurred No. (%)	
A	▲	▲	87 (27.3)	**18 (20.7)**	
B	▲	WNL	97 (30.4)	14 (14.4)	*0.010*
C	WNL	▲	18 (5.6)	3 (16.7)	
D	WNL	WNL	117 (36.7)	**6 (5.1)**	

pCEA: intraperitoneal carcinoembryonic antigen, WNL: within normal limits, Pt: patient, POD: postoperative day

3.5 Survival analysis

Recurrence free survival was analyzed according to pCEA levels in POD1 according to cox regression model, five-year recurrence-free survival was 91.5% for WNL pCEA group and 84.7% for elevated group (p=0.073) (Figure 2). Among different patterns of pCEA over the postoperative period, as seen on Figure 3, 5-year RFS tended to be the lowest for A (elevated within POD1 and

continued to be elevated at POD5) and the highest for D (pCEA always WNL), 77.6% vs 91.2% respectively, p=0.074). Overall survival analysis showed no significant differences between WNL and elevated pCEA at POD1 (95.7% vs. 92.9%, respectively, p=0.276) (figure 4).

Figure 2. Recurrence-free survival graph for POD1 pCEA

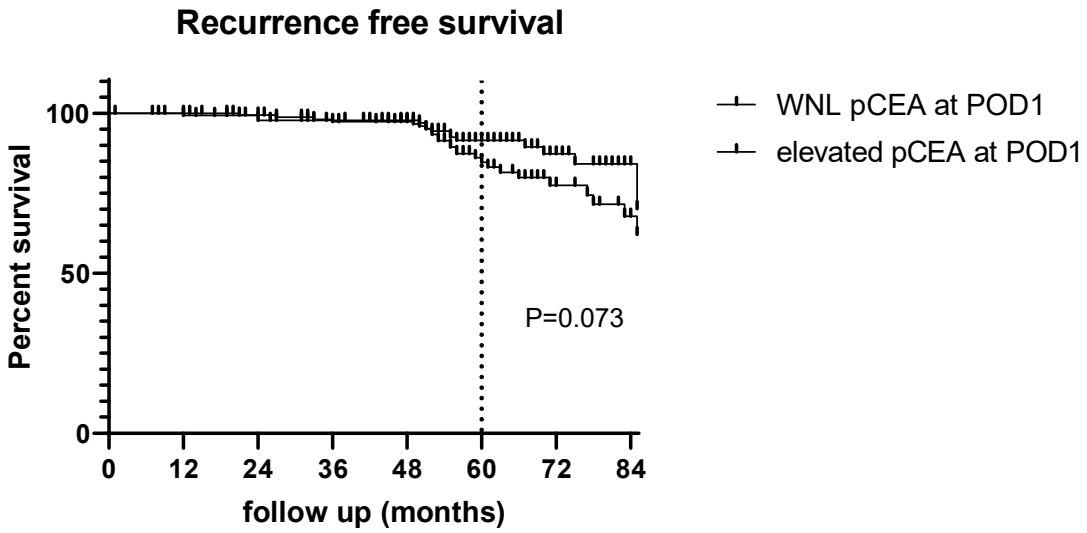


Figure 3. Recurrence-free survival graph for different pCEA change pattern

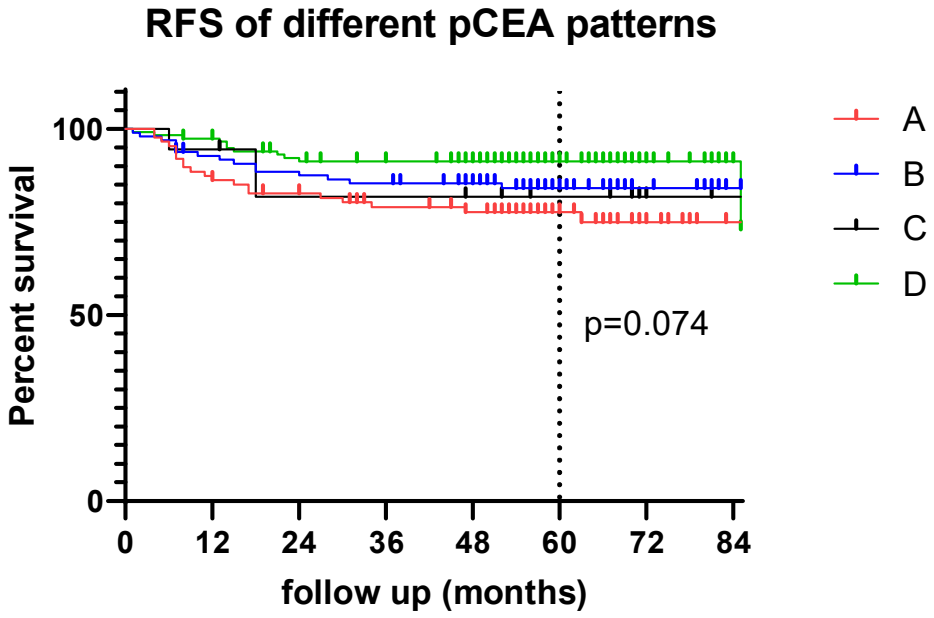
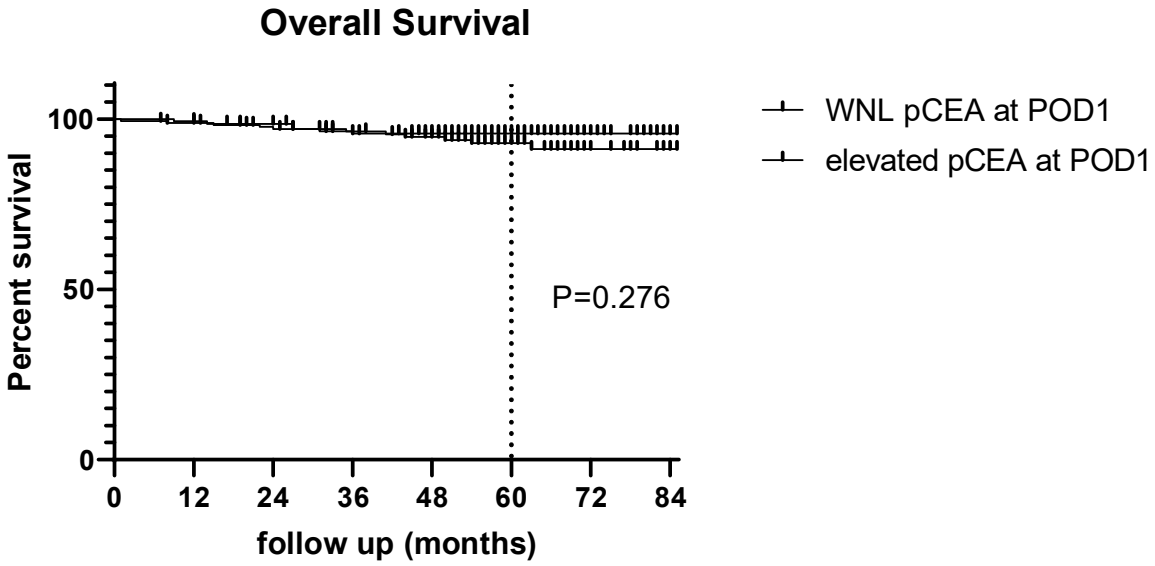


Figure 4. Overall survival graph for POD1 pCEA



4. Discussion

Our study results showed that elevated CEA levels in the postoperative drainage fluid (pCEA) within the first postoperative day in patients who underwent curative resection for colorectal cancer were significantly associated with an increased risk of recurrence on multivariate analysis. Other significant factors associated with recurrence were lymph node metastasis and choosing minimally invasive methods. Furthermore, patients with elevated pCEA levels had a shorter recurrence-free survival (RFS) compared to those with normal pCEA levels. To our knowledge, this study is the first to examine the relationship between serially measured pCEA levels with risk of recurrence in colorectal cancer patients.

First, to assess the causal relationship of pCEA with other perioperative factors that might directly influence recurrence risk, we compared the levels of pCEA with various perioperative factors such as lymph node metastasis and the use of minimally invasive methods and did not find any remarkable difference between two groups (supplementary table 1). Between normal vs. elevated pCEA group on POD1, basic patient characteristics and tumor location were found to be comparable, there were more patients with elevated sCEA (6.9% vs. 39.3%, $p<0.001$), larger tumor size (median 2.5cm vs. 3.5cm, $p=0.025$), longer proximal and distal margins (proximal 10.0cm vs. 11.0cm, $p=0.001$) and (distal 5.0cm vs. 5.5cm, $p<0.001$). Longer margins can be attributed to the fact that tumor size was slightly larger, encouraging surgeons to resect at a further point. However, there was no difference in preoperative symptoms such as obstruction requiring stent insertion, or signs of bleeding ($p=0.373$), nor in harvested LNs ($p=0.583$), positive LNs ($p>0.99$), and postoperative complications ($p=0.380$).

In theory, having elevated pCEA following curative intent resection of primary cancer might indicate residual disease or represent the extent of disease that was overlooked from preoperative diagnostic modalities. On our subgroup analysis conducted between colon and rectal cancer patients, significant association found between elevated pCEA with recurrence was only found in rectal cancer patients. One possible explanation, which can also be a limitation in our study is that drainage tubes were found to be placed mostly in pelvic cavity, which is right at the operation field and adjacent to anastomosis in rectal cancer patients. although ascitic fluids circulate within the

peritoneal cavity, it is possible that drainage fluid from the pelvic cavity may more accurately reflect the local tumor microenvironment of rectal cancer.

Elevated serum CEA level, however, did not show significant association with recurrence risk and RFS. Also, patients who had elevated pCEA but had normal sCEA preoperatively showed higher recurrence rates that those who did not have pCEA elevation although it did not reach statistical significance (16.9% vs. 10.1%, p=0.088). Such findings support our notion that monitoring pCEA levels in postoperative drainage fluid may provide adequate information to fill in the gap of limits of sCEA in foreseeing disease recurrence.

Comparison between the four different patterns of pCEA measured throughout the postoperative periods revealed that patients with consistently elevated pCEA had the highest risk of recurrence, followed by those with intermittent elevation, and consistently normal pCEA had the lowest recurrence rate (Figure1). Previous studies regarding pCEA or preoperative cytology in colorectal cancer have tried to find association between elevated pCEA level checked at one time point with specifically peritoneal metastasis or disease recurrence[6]. However, our study expands on this by examining the patterns of pCEA levels over time and their association with recurrence risk.

Limitations of sCEA in providing more precise and early prediction of recurrence in colorectal cancer patients have driven researchers to explore alternative markers. Aside from CEA measurement in alternative sources like our study, one such alternative is circulating tumor DNA[7, 8]. some of the earlier results involving ctDNA were focused on metastatic disease and its potential in verifying response to treatment. However, newer research supports the concept of ctDNA detection for minimal residual disease extent in curative setting and further application to general population for early cancer diagnosis[9].

On the other hand, some evidence and viewpoints highlight some concerns and challenges of clinical application of ctDNA.[10] These concerns include the need for standardized methods for ctDNA detection, the potential for false-positive results due to clonal hematopoiesis or non-ccancer-related mutations, and the limitations of ctDNA detection in certain cancer types. Furthermore, ctDNA is not yet widely available and is still considered a research tool rather than a routine clinical test [11], and it is important to note that further studies are needed to fully understand the clinical utility and potential limitations of ctDNA as a biomarker for recurrence in colorectal cancer. A recent study by

Fakih et al (2022)[12] comparing surveillance strategies of ctDNA, imaging and CEA levels in patients with resected colorectal cancer reported that CEA measurement combined with imaging studies has proven to be more sensitive and efficient modality than ctDNA testing. CEA measurement is currently widely accessible, and has been for many decades, relatively inexpensive, and has established clinical utility in monitoring colorectal cancer patients for recurrence. Mixed results about the alternative choices of biomarkers combined with limited sensitivity of sCEA levels have prompted the importance of utilizing multiple modalities in order to accurately predict recurrence in colorectal cancer patients and tailor surveillance accordingly.

Although our study has shone some light on the potential use of carcinoembryonic antigen levels in ascites for predicting recurrence in colorectal cancer patients, it has some limitations. the retrospective nature of study has limited detailed analysis of the relationship between elevated pCEA level with recurrence. Failure of colon cancer subgroup to show statistical significance in predicting recurrence using CEA levels in ascites suggests the need for further investigation and larger studies in this specific population. Also, the range of CEA levels in peritoneal drainage fluid was wider than seen in serum sample measurements, which may have influenced our ability to identify a specific cutoff value for predicting recurrence. we decided on the cutoff value of 5ng/mL same as serum sample levels as similar researches did so, but further research is needed to validate this cutoff value in ascites fluid.

5. Conclusion

In conclusion, the use of carcinoembryonic antigen levels in ascites in immediate postoperative period shows potential as a biomarker for predicting recurrence in rectal cancer patients. We believe that utilizing elevated pCEA as an indicator for need of tighter surveillance and closer follow-up in these patients.

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Appendix 1.

Supplementary table 1. Comparison of Patients' perioperative characteristics and relationship to peritoneal CEA elevation on immediate postoperative sample (POD0)

	WNL pCEA	**Elevated pCEA**	***P***
	N (%), median (IQR)		
BMI	23.6 (3.49)	23.2 (3.23)	
Minimally invasive surgery	110 (94.8)	167 (96.5)	*0.553*
Preoperative symptoms†	3 (2.6)	9 (5.2)	*0.373*
Elevated sCEA	8 (6.9)	68 (39.3)	***<0.001***
Lesion location			*0.323*
Colon	69 (59.5)	113 (65.3)	
Rectum	47 (40.5)	60 (34.7)	
Neoadjuvant CRT	32 (27.6)	54 (31.2)	*0.600*
Specimen extracted via anus	9 (7.8)	6 (3.5)	*0.174*
Estimated blood loss (mL)	50 (20-150)	50 (20-100)	*0.865*
Operation time (min)	237 (183-289)	237 (189-300)	*0.259*
Tumor size (cm)	2.5 (1.5-3.8)	3.5 (2.2-5.3)	***0.025***
Proximal margin	10.0 (7.0-12.0)	11.0 (7.0-15.0)	***0.001***
Distal margin	5.0 (3.0-7.0)	5.5 (3.0-15.0)	***<0.001***
Harvested LNs	16 (12-21)	21 (15-30)	*0.583*
Positive LNs	0 (0-1)	0 (0-1)	*>0.99*
Total hospital stay (days)	7 (6-9)	7 (6-8)	*0.309*
Postoperative complication	7 (6.0)	16 (9.2)	*0.380*

WNL: within normal limits, pCEA: peritoneal drainage carcinoembryonic antigen, sCEA: serum CEA, IQR: interquartile range, BMI: body mass index, CRT: chemoradiotherapy, LNs: lymph nodes

† preoperative symptoms: obstructive symptoms requiring stent insertion, gastrointestinal bleeding

Appendix 2.

Supplementary table 1. Comparison of Patients' perioperative characteristics and relationship to peritoneal CEA elevation on first postoperative day sample (POD1)

	WNL pCEA	**Elevated pCEA**	***P***
	N (%), median (IQR)		
BMI			*0.275*
Minimally invasive surgery	166 (95.4)	134 (95.7)	*>0.99*
Preoperative symptoms†	6 (3.4)	7 (5.0)	*0.574*
Elevated sCEA	23 (13.2)	56 (40.0)	***<0.001***
Lesion location			*>0.99*
Colon	109 (62.6)	88 (62.9)	
Rectum	65 (37.4)	52 (37.1)	
Neoadjuvant CRT	50 (28.7)	44 (31.4)	*0.622*
Specimen extracted via anus	11 (6.3)	6 (4.3)	*0.464*
Estimated blood loss (mL)	50 (20-100)	50 (20-100)	*0.060*
Operation time (min)	239 (189-300)	240 (188-309)	*0.202*
Tumor size (cm)	2.9 (2.0-4.1)	3.7 (2.1-5.4)	***0.013***
Proximal margin	10.0 (7.0-13.0)	10.0 (7.0-15.0)	***0.033***
Distal margin	5.0 (3.0-8.0)	5.0 (3.0-12.0)	***<0.001***
Harvested LNs	18 (12-26)	21 (15-29)	*0.607*
Positive LNs	0 (0-1)	0 (0-2)	*0.053*
Total hospital stay (days)	7 (6-9)	7 (6-9)	*0.672*
Postoperative complication	9 (5.2)	16 (11.4)	*0.058*

Appendix 3

Supplementary table 3. Subgroup analysis between Colon/Rectal cancer for recurrence risk assessment – colon cancer cohort

	Univariate	Multivariate		
	P	HR	95%CI	P
Age > 50	0.730			
Male	0.812			
MIS op	0.239			
Tumor size≥3cm	0.283			
Right colon	**0.044**	1.94	0.77-4.92	>0.99
pT≥3	**0.028**	3.08	0.66-14.40	0.071
Node metastasis	**<0.001**	6.19	2.19-17.46	**0.001**
*Pre-op complication	0.396			
Pre-sCEA ▲	0.565			
POD7-sCEA ▲	0.738			
pCEA POD 0 ▲	0.090			
pCEA POD 1 ▲	**0.040**	1.76	0.67-4.62	0.111
pCEA POD 5 ▲	0.409			

MIS: minimally invasive surgery, pT: pathologic T stage, sCEA: serum carcinoembryonic antigen, pCEA: intraperitoneal CEA, POD: postoperative day

* Pre-op complication: symptomatic obstruction requiring stent insertion, gastrointestinal bleeding

Appendix 4

Supplementary table 4. Subgroup analysis between Colon/Rectal cancer for recurrence risk assessment – rectal cancer cohort

	Univariate	Multivariate		
	P	HR	95%CI	P
Age > 50	0.292			
Male	0.426			
MIS op	**0.030**	0.04	0.01-0.46	**0.010**
Tumor size≥3cm	0.721			
pT≥3	**0.057**	0.81	0.20-3.24	0.780
Node metastasis	**0.004**	4.99	1.46-17.08	**0.011**
*Pre-op complication	0.394			
Pre-sCEA ▲	0.126			
POD7-sCEA ▲	0.786			
pCEA POD 0 ▲	**0.038**	7.82	1.54-39.55	**0.013**
pCEA POD 1 ▲	**0.014**	1.19	0.26-5.53	0.842
pCEA POD 5 ▲	0.210			

MIS: minimally invasive surgery, pT: pathologic T stage, sCEA: serum carcinoembryonic antigen, pCEA: intraperitoneal CEA, POD: postoperative day

* Pre-op complication: symptomatic obstruction requiring stent insertion, gastrointestinal bleeding

Abstract in Korean

수술 직후 복강 내 체액에서 관찰된 종양표지자 CEA의 수치와 직장암의 근치적 수술 후 재발과의 연관성에 대한 탐색적 연구

결장 및 직장암은 전 세계적으로 암 관련 사망의 주요 원인 중 하나로 여전히 자리매김하고 있으며, 그 원인으로는 원발암의 근치적 수술 이후의 원격전이 및 재발을 들 수 있습니다. 현재 결장 직장암 환자의 추적관찰에 활용되는 진단 바이오마커인 carcinoembryonic antigen (CEA)는 혈청에서 측정한 수치를 기준으로 (sCEA) 단독으로 사용할 때 민감도 및 특이도가 부족한 것이 문제점으로 꼽을 수 있는데, 이를 보완할 수 있는 대체 바이오마커나 대체 검사 방법 등에 대한 관심도는 높아지는 추세입니다. 본 연구에서는 대장직장암의 수술 후 재발의 예후 지표로서 수술 후 배액되는 체액에서 측정한 CEA 수치의 가능성에 대해 조사하고자 하였습니다.

2014년 7월부터 2018년 11월까지 결장 및 직장암에 대한 근치적 절제술을 받은 319명의 환자를 대상으로 후향적인 분석을 통해 기본 특징, 수술관련 결과, 수술 후 재발 등에 대해 살펴보았습니다. 주로는 복강 내 체액의 CEA 수치 (pCEA) 과 재발율, 생존율 (recurrence-free survival) 등을 분석하였습니다.

수술 후 1일 이내에 측정된 CEA 수치는 재발 위험 증가와 유의한 상관관계를 보였습니다 (OR 3.10, 95% CI 1.54-6.24, p=0.002). 다변량 분석에서 림프절 전이 및 최소 침습수술 또한 유의한 상관관계를 보였지만 sCEA 와의 연관은 본 연구에서는 관찰할 수 없었습니다. 직장암 환자들만 따로 분석한 결과 결장암 환자들보다 수술 후 pCEA 증가와 재발 간의 강한 관련성을 보였습니다.

본 연구의 결과들을 토대로 수술 후 배액관을 통해 쉽게 얻을 수 있는 복강 내 체액에서의 CEA 수치 측정 값은 (pCEA) 1일 이내에 상승을 보이는 경우 직장암의 재발 위험도가 높은 것을 알 수 있었으며 이는 현재 쓰이는 수술 전 측정된 sCEA의 수치보다 더 유용한 예후 인자로서 참고할 수 있을 것이라 생각합니다.

핵심되는 말: 대장암, 종양지표자, 수술 후 배액관