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□ 원 저 □

CEA Study on the Effect of the No-touch Isolation Technique for Preventing Tumor Metastasis in Patients with Colorectal Cancer

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Purpose: Although the 'No-touch' isolation technique was introduced by Turnbull et al. in 1967, the controversy over whether or not it reduces the risk of metastasis during surgery exists even today. The aim of this study was to evaluate the effect of the 'No-touch' isolation technique in primary colorectal cancer surgery.

Methods: The evaluation was done by comparing the levels of CEA and CEA m-RNA expression from the same draining vein before and after tumor mobilization. Blood samples from 25 patients with primary colorectal cancer were collected for analysis. At the time of surgery, the main draining vein from the tumor was isolated and ligated at the proximal end. The 1st blood samples were collected just prior to tumor mobilization, and the 2nd samples right after. Both samples were analyzed for serum CEA level and CEA mRNA expression by using reverse transcriptase polymerase chain reaction (RT-PCR).

Results: The mean CEA value from draining veins after tumor mobilization (8.08±8.98 ng/ml) was significantly higher than it was before mobilization (4.17±4.98 ng/ml). CEA mRNA was detected in 16% (4/25) of the blood specimens post-mobilization, whereas it was detected in only 4% (1/25) of the pre-mobilization samples.

Conclusions: The results suggest the validity of using the 'No-touch' isolation technique to reduce the risk of metastasis into the draining vein during mobilization. J Korean Soc Coloproctol 2004;20:105-111

Key Words: Carcinoembryonic antigen, No-touch isolation technique, Colorectal neoplasm
암태아성항원, No-touch isolation technique, 대장암

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INTRODUCTION

Colorectal cancer can spread via direct extension, lymphatic channels, and the blood stream. Distant metastasis remains as one of the major causes of death for colorectal cancer, and many treatment efforts focus on reducing the risk or, at least, on delaying the development of metastatic diseases.

It has been recognized for many years that an ineffective surgical technique can add to the risk of distant metastasis during surgery. Controversy surrounding the usefulness of the 'No-touch' isolation technique introduced by Turnbull et al[1] in 1967 was the major impetus for the current study. Confirmation of the usefulness of the technique was done by measuring the CEA levels and the CEA mRNA expressions by using the RT-PCR technique on blood samples taken from the major draining veins of the tumor before and after tumor mobilization. The CEA marker was chosen because it correlates well with clinical tumor recurrence and the survival rate and because it has relatively higher concentration in colorectal cancer tissue than it does in normal tissue.[2]

METHODS

Blood samples from 25 patients who underwent surgical resection for primary colorectal cancer were collected for CEA and CEA mRNA analysis. All patients had their surgery at Keimyung University Dongsan Medical Center between January 2000 and July 2001.

Lymphovascular dissection was carried out, and the main draining veins from the tumor were isolated prior to tumor mobilization. The veins were ligated, and the 1st blood samples were taken from the proximal end of the draining vein after ligation. The 2nd blood samples were taken from the same site prior to the removal of the tumor after full mobilization of the tumor. Patients with a metastatic mass around the draining vein, multiple or recurrent colon cancer, a history of prior chemotherapy or radiotherapy, ambiguous draining veins, a tumor less than 3 cm were excluded from the study. Also, patients with mesocolon invasion were excluded because of the anticipated difficulty in tumor mobilization. Eight hemorrhoids patients were studied as a negative control. The statistical significances of differences were determined by using the chi-square and the student T test.

1) Operation Methods

For right-sided colon cancers, we first identified the superior mesenteric vein, dissected it from the distal to the proximal site, and ligated the ileocolic and the right colic veins. We removed the visible lymph nodes around the draining vessels at the origins on the superior mesenteric vessels. Tumor mobilization followed after complete removal of the lymphovascular field. For left-sided and sigmoid rectal cancers, the surgical procedure began at the bifurcation and proceeded to the origin of the inferior mesenteric artery (IMA), which was ligated at its origin. Finding and ligating the draining veins from the right, the left, and the sigmoid colon were usually easy, but that was not the case with rectal lesions (especially low-lying ones) because of the difficulty in approaching the deep pelvic cavity. For this reason, blood samples for a rectal lesion were taken from the superior hemorrhoidal vein. The superior hemorrhoidal artery just distal to the origin of the left colic artery was ligated, and all possible metastatic lymph nodes between the origin of the IMA and the division of the left colic artery was cleared. In case of a low rectal cancer, a high ligation of the IMA at the origin was done, and a full mobilization of the descending colon was made to prevent anastomotic tension. We removed all visible lymph nodes. A tumor mobilization was also done after a lymphovascular dissection.

2) RNA Preparation and cDNA Synthesis

Total blood cells were extracted from 5 ml of blood, and were mixed with the same amount of ACK lysis buffer. RNA was obtained by using the thiocyanate, phenol-chloroform method described by Chomczynski and Sacchi.[3] To ensure RNA purity for the RT-PCR, we carried out a PCR assay with primers specific for the gene GAPDH cDNA in each case. The sequence of primers for GAPDH was as follows:

GAPDH primer

sense: 5'-CGTCTTCACCACCATGGAGA-3'

antisense: 5'-CGGCCATCACGCCACAGTTT-3'.

cDNA was synthesized from 2㎍ of total RNA in a 2㎕ reaction mixture containing 4㎕ of reverse transcriptase buffer (5X), 0.5 15㎕ of 10 mM dATP, 0.5 ㎕ of 10 mM dGTP, 0.5㎕ of 10 mM dTTP, 0.5㎕ of 10 mM dCTP, 0.5㎕ of MMLV reverse-transcriptase, and 0.5㎕ of RNAse inhibitor. The mixture was placed at room temperature for 10 min and then was heated at 42°C for 60 min.

3) Assesment of Sensitivity of Nested RT-PCR

SNU C1 (colon cancer cells) were cultured in RPMI 1640 containing fetal bovine serum 10%, antibiotics, and antimycotics (Gibco BRL). From 10 to 10^5 serially diluted SNU C1 cells were mixed in 5 ml of normal human blood. CEA mRNA could be detected at the level of 10 cells in 5 ml of normal blood by using nested RT-PCR (Fig. 1).

4) Nested RT-PCR

The sequences of the genes studied were obtained from GenBank, and the primers were designed. The CEA-specific oligonucleotide primers used for nested PCR

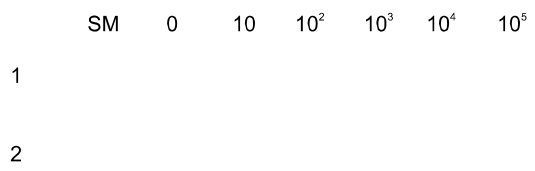

Fig. 1. Assessment of the sensitivity of nested RT-PCR. CEA mRNA could be detected at the level of 10 cells in 5 ml of normal blood by using nested RT-PCR (SM: Size marker, 100 bp ladder; 1: RT-PCR; 2: nested RT-PCR).

were as follows (Fig. 2).

CEA first PCR primer

1. sense: 5'-TCACAGTCTCTGCATCTGGA-3'
2. antisense: 5'-GCTTGATCTTGGTGGACAGT-3'

CEA second PCR primer

3. sense: 5'-CTCTGCATCTGGAACTTCTC-3'
4. antisense: 5'-TCTTGCTCTGTTGCCAGACT-3'

For the first PCR, 20㎕ containing 2㎕ 10X PCR buffer, 1.2㎕ 25 mM $MgCl_2$, 0.2㎕ 10 mM dATP, 0.2㎕

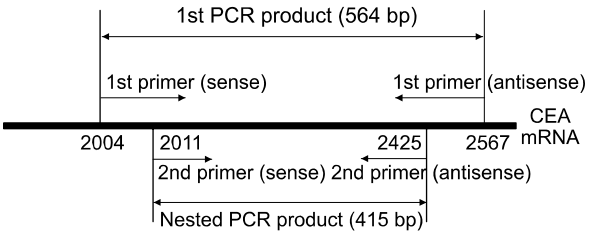

Fig. 2. CEA-specific oligonucleotide primers used for nested PCR.

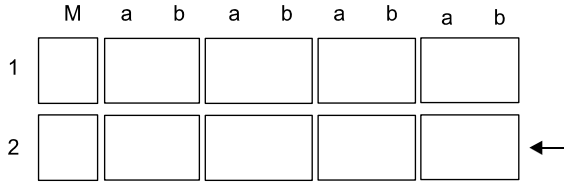

Fig. 3. Detection of CEA message in blood of colon cancer patients by nested RT-PCR. Blood samples were obtained at draining vein before cancer mobilization (a), after mobilization (b). (M: Size marker, 100 bp ladder, 1: GAPDH, 2: CEA).

Table 1. Characteristics of the patients

Patient	Sex	Age	Location*	Stage†	Size‡	vl§	CEA m-RNA‖	s CEA¶
1	F	62	R	2	5	N	-	+
2	M	63	C	3	8	Nc	+	+
3	F	45	R	2	8	N	-	+
4	M	64	C	2	10	N	-	-
5	F	64	C	2	3	T	+	+
6	M	62	C	2	8	Nc	-	-
7	F	70	R	2	5	T	-	+
8	F	54	C	3	10	T	-	+
9	M	60	R	3	5	T	-	+
10	M	60	R	3	5	T	-	-
11	F	40	C	3	4	T	-	+
12	M	74	R	3	4	N	-	+
13	M	34	C	3	4	Nc	-	+
14	M	62	C	2	5	N	-	+
15	F	59	R	2	3	N	-	-
16	F	64	C	3	5	T	-	+
17	M	59	R	2	5	T	-	+
18	M	39	R	2	3	N	+	-
19	F	42	C	2	4	T	-	+
20	M	61	C	2	8	Nc	-	+
21	M	68	C	2	8	N	-	+
22	M	56	R	2	5	N	-	+
23	M	49	C	2	9	N	-	+
24	F	42	C	4	4	T	-	+
25	F	42	R	3	5	N	-	+

*Location = anatomic location of the tumor (R: rectum, C:colon); † Stage = UICC TNM classification at diagnosis; ‡ Size = the largest diameter of tumor (cm); §vl = vessel invasion (n: no invasion, t: invasion, nc: no available data); ‖CEA m-RNA (+) = positive expression in tumor draining blood after mobilization, but negative expression before mobilization; ¶s CEA (+) = the CEA value of the draining veins after tumor mobilization was significantly higher than it was before mobilization.

Table 2. Comparison of CEA mRNA expressions and serum levels of CEA before and after tumor mobilization

	Before	After	P-value
Serum CEA(ng)	4.17±4.98	8.08±8.98	0.035
RT-PCR	1/25 (4%)	3/25 (12%)	0.000

Table 3. Comparison of CEA mRNA expressions and serum levels of CEA according to stage

	Stage 2	Stage 3, 4	P
CEA m-RNA (+)*	2/15 (13.3%)	1/10 (10%)	0.645
s CEA (+)†	11/15 (73.3%)	9/10 (90%)	0.313

*CEA m-RNA (+) = positive expression in tumor draining blood after mobilization, but negative expression before mobilization; † s CEA (+) = the CEA value of draining veins after tumor mobilization was significantly higher than it was before mobilization.

10 mM dGTP, 0.2㎕ 10 mM dTTP, 0.2㎕ 10 mM dCTP, 0.1㎕ Taq polymerase (Promega Co., USA), 50㎛M sense, and 0.1㎕ each of primers 1 and 2 were added to the ependorph tube. Thirty cycles of amplification were performed in a theromocycler (Cetus 480, Perkin Elmer Co., USA). The conditions for each cycle were 94°C for 5 minutes, 94°C for 30 seconds, 57°C for 45 seconds, and 72°C for 45 seconds with a final extension step for 5 minutes.

For the second PCR, the 1st PCR product was used as a template. PCR products were electrophoresed on 1% agarose gel. The conditions were the same as those for the 1st PCR. The first PCR product exhibited a 564 bp fragment, and the second PCR product exhibited a 415 bp fragment (Fig. 3).

RESULTS

The mean CEA value from the draining veins after tumor mobilization (8.08 ng/mL) was significantly higher than it was before mobilization (4.17 ng/mL). CEA mRNA was detected in 16% (4/25) of the after- mobilization group and in 4% (1/25) of the before-mobilization group (Fig. 2, Table 1, 2). We did not find any correlations when comparing the CEA mRNA (+) group and the serum CEA (+) group according to the tumor stage (Table 3) and tumor location (Table 4). CEA m-RNA (+) means a positive expression in the tumor draining blood after mobilization, but negative expression before mobilization. Serum CEA (+) means the CEA value of the draining veins after tumor mobilization was significantly higher than it was before mobilization.

Table 4. Comparison of CEA mRNA expressions and serum levels of CEA according to tumor location

	CEA m-RNA (+)*	s CEA (+)†
Colon	2/14 (14.3%)	12/14 (85.7%)
Rectum	1/11 (9.1%)	8/11 (72.7%)
P	0.593	0.378

*CEA m-RNA (+) = positive expression in tumor draining blood after mobilization, but negative expression before mobilization; † s CEA (+) = The CEA value of draining veins after tumor mobilization was significantly higher than it was before mobilization.

DISCUSSION

Animal studies have shown that malignant cells are shed into draining blood veins during manual manipulation of a primary tumor, which could augment the chance for distant metastasis.[4,5] In 1967, Turnbull suggested that operative manipulation of a cancer-bearing segment of colon would increase the incidence of fatal metastasis and that the five-year survival rate for stage-C colon cancer patients could be prolonged by using the 'No-touch' isolation technique.[1] However, there has been much controversy surrounding the actual beneficial effects of Turnbull's 'No-touch' isolation technique in preventing distant metastasis.[6] In 1952, Barnes[7] found that the blood and the lymph channels of a cancer lesion should be severed before manipulating the cancer itself. A similar finding was confirmed in a prospective randomized study by Wiggers et al.[8] Stearns & Schottenfeld[9] stressed the importance of a wide resection of the mesentery in the involved area and recommended the practice of Turnbull's 'No-touch' technique as long as it did not interfere with the wide resection. However, they stressed that Turnbull had compared his technique with conventional resections done by other members of his clinic and that minimal

manipulation of the tumor should be practiced as much as possible, but should not interfere with the primary essential of wide removal of the mesentery of the cancer-bearing bowel segment.[9] Enker et al. showed that performing a wide anatomic dissection with complete lymphadenectomy was more important than the order of operative procedures in achieving a better five-year survival rate.[10]

There are number of problems in comparing the results of Turnbull's technique with those of other control groups. The best way to assess the impact of Turnbull's technique would be to compare groups operated on by the same surgeon, with colorectal tumors being mobilized either with or without the 'No-touch' isolation technique. This, however, could pose an ethical problem because early lymphovascular isolation prior to tumor mobilization is a well-established technique in colorectal surgery. In order to study this objectively without an ethical problem, CEA and its mRNA expression levels were used as surrogate markers for the presence of tumor cells. Though it has long been postulated that manipulation of malignant tumors encourages tumor-cell dissemination,[11] it is difficult to prove distant metastasis occur as a result of tumor cells disseminated during surgery. Conversely, the benefit of the 'No-touch' technique in terms of survival improvement is even more difficult to prove. Liver metastases in colorectal cancer are usually from hematogenous spread via the draining veins from the primary tumor.[12] Cancer-cell invasion into the portal vein is more frequently associated with liver metastasis in colorectal cancer. Many colorectal cancer patients die of liver metastasis after surgery. Therefore, during surgery, it is imperative to reduce the risk of liver metastasis.

Cancer cells may reach the liver through the superior mesenteric or inferior mesenteric vein during manipulation of the tumor at the time of surgery. However, whether these disseminated malignant cells can actually grow in the liver is uncertain because studies with other organs have shown that a quite large number of tumor cells from draining veins are necessary for successful implantation. Manipulation of the tumor has been shown to facilitate shedding of tumor cells into blood vessels. Although checking for circulating tumor cells is feasible by using conventional cytology, immunocytochemistry, and MASA (mutant-allele-specific amplification) in patients undergoing resection for colorectal cancer,[13,14] it is cumbersome and quite difficult. Recently, the RT-PCR technique has become popular because it can be easily used even with a minute amount of tumor sample. Many researchers have tried to verify the shedding of tumor cells after tumor manipulation using the RT-PCR technique to check for various genes.[5,15] Although many colorectal cancer-related genes have been studied, no gene - specific enough for the diagnosis of CRC - has been identified.

The confirmation of increased expression of CEA mRNA in tumor-draining veins provides us with insightful information on tumor shedding.[11,16] Four out of the 25 (16%) post-mobilization samples showed CEA mRNA expression, compared with one out of the 25 (4%) pre-mobilization samples in our study. Kanoh et al.[17] Reported that the CEA levels in lymph nodes appeared to be influenced by its concentrations in the tumor-draining vessels. Also, the CEA level in metastatic lymph nodes was found to be significantly higher than it was in neighboring lymph nodes without metastatic disease. Mun et al.[18] reported that after tumor manipulation, the CEA levels in the portal vein were higher than those in the peripheral vein. Our data showed that the mean CEA value in the draining veins after tumor mobilization was significantly higher than the pre-mobilization value. Although the survival and the recurrence rates for our study group were not compared to those of a conventional surgery group, our results suggest that the use of early lymphovascular dissection may contribute to reducing the potential risk of tumor-cell dissemination into draining veins and to the liver at the time of surgery.

In conclusion, our results seem to support the assertion that early lymphovascular ligation is superior to conventional surgery in terms of reducing the risk of potential tumor-cell dissemination during surgery. Although a few of the tumor cells may survive in the blood stream, this procedure is sure to lessen the possibility of cancer cells invading the liver via the draining veins during surgery. Early lymph node dissection and ligation of draining veins before manipulating the tumor are crucial operative steps in reducing the potential risk of metastasis into draining veins in colorectal cancer. Further study based on the survival and the recurrence rates is necessary to

confirm the effect of this procedure.

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국문 초록

대장암에서 No Touch Isolation 술식이 종양전이 방지에 미치는 영향에 관한 CEA 연구

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목적: ‘No-touch’ isolation 술식은 아직까지도 술 중 전이의 위험도를 낮추는가에 대해서는 논란의 대상이 되고 있다. 이 술식의 재발률을 분석하기 위해 가장 이상적인 연구방법은 단일기관의 단일 술자에 의해 기존의 술식과 비교하여 연구하는 것이 바람직하지만, 어려움이 있다. 저자들은 대장암에서 이 술식의 종양 조작 전 혈관결찰술이 암전이 위험성을 저하시킬 수 있는가를 실험적 방법으로 확인하고자 본 연구를 시작하였다.

대상 및 방법: 25예의 대장암 환자에서 술 중 종양 조작이 이루어지기 전에 주 배액 정맥을 분리하여 결찰을

하였으며, 종양 조작 전 후에 주 배액 정맥을 통해 각각 정맥혈 채취를 하였다. 이들 정맥혈에서 혈청 CEA 수치 및 RT-PCR을 이용한 CEA m-RNA의 발현 여부를 비교 분석하였다.

결과: 종양 조작 후에 이루어진 배액 정맥혈에서의 평균 혈청 CEA 수치는 8.08±8.98 ng/ml로 종양 조작 전의 평균 혈청 CEA 수치인 4.17±4.98 ng/ml보다 유의하게 증가하였으며(P=0.035), CEA m-RNA의 발현은 종양 조작 후의 정맥혈에서 16% (4/25)로, 종양 조작 전의 정맥혈에서 4% (1/25)보다 유의하게 증가하였다 (P=0.00).

결론: 'No-touch' isolation 술식 중 종양 조작 전 혈관결찰술은 대장암 세포전이의 위험성을 낮출 수 있는 것으로 생각이 되지만, 술 후 재발률, 사망률 등의 임상적 연구가 더 필요할 것으로 생각된다.

편집인의 글

대장암 수술 시 No-touch isolation술기는 종양세포의 전신성 이탈을 예방할 수 있다는 이론적 배경과 함께 그 효과면에서는 재발 및 예후와 관련한 연구상 지속적으로 논란이 제기되고 있다. 저자는 객관적인 검증방식으로 대장종양 표식자로 가장 의미 있으며 생물학적 성질이 잘 알려진 암태아성항원(CEA) 당단백과 mRNA를 대장암 수술 시 종양기동 전후를 통해 비교 분석하였으며 의미있는 변화를 관찰하여 No-touch isolation술기의 타당성을 제시하였다. 세포조직학 및 분자생물학적 방식을 적용한 기존연구에서 수술 후 조직액 및 혈액에 존재하는 잔여암은 재발 및 예후와 깊은 관련을 보이는 것으로 알려져 있다. 대장암에서 CEA 과잉발현은 세포간 및 세포-기질간 상호작용, 신호전달, 세포이동 및 면역억제의 생물학적 기전을 통해 종양의 진행 및 전이를 촉진하는 것으로 알려져 있다. CEA는 정상 소화기 상피에서도 분비되지만 그 양이 매우 적으며 소화기암의 혈청내 CEA는 종양세포에서 특이적으로 분비되는 것으로 이해되므로 본 연구의 그 적용은 타당하다. 향후 연구에서 대상군 설정 시 유입 정맥혈이 전신성 경로를 동반하는 직장암을 제외시키고, 대조군으로서 No-touch isolation술기를 적용하지 않은 군을 추가하면 보다 완벽한 객관적 결론도출이 가능하겠으며 이외, 이미 분비된 CEA의 반감기가 4~5일인 점을 감안해서 본 기간을 포함한 수술 전후 지속적인 혈청 CEA 측정치의 비교를 추가한 연구결과를 기대한다.

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