Differentiation of Recurrent Rectal Cancer and Postoperative Fibrosis: Preliminary Report by Proton MR Spectroscopy

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Purpose : To know the differences of proton MR spectroscopic features between recurrent rectal cancer and fibrosis in post-operative period, and to evaluate the possibility to discriminate recurrent rectal cancer from post-operative fibrosis by analysis of proton MR spectra.

Materials and Methods : We evaluated the proton MR spectra from 25 soft tissue masses in perirectal area that developed in post-operative period after operation for the resection of rectal cancer. Our series included 11 cases of recurrent rectal cancer and 14 of fibrotic mass. All cases of recurrent rectal cancer and post-operative fibrosis were confirmed by biopsy. We evaluated the spectra with an attention to the differences of pattern of the curves between recurrent rectal cancer and post-operative fibrosis. The ratio of peak area of all peaks at 1.6-4.1ppm to lipid (0.9-1.6ppm) [P (1.6-4.1ppm)/P (0.9-1.6ppm)] was calculated in recurrent rectal cancer and post-operative fibrosis groups, and compared the results between these groups. We also evaluated the sensitivity and specificity for discriminating recurrent rectal cancer from post-operative fibrosis by analysis of ^{1}H-MRS.

Results : Proton MR spectra of post-operative fibrosis showed significantly diminished amount of lipids compared with that of recurrent rectal cancer. The ratio of P (1.6-4.1ppm)/P (0.9-1.6ppm) in post-operative fibrosis was much higher than that of recurrent rectal cancer with statistical significance ($p < .05$) due to decreased peak area of lipids. Mean (standard deviations of P (1.6-4.1ppm)/P (0.9-1.6ppm) in post-operative fibrosis and recurrent rectal cancer group were 2.71 ± 1.48 and 0.29 ± 0.11, respectively. With a cut-off value of 0.6 for discriminating recurrent rectal cancer from post-operative fibrosis, both the sensitivity and specificity were 100% (11/11, and 14/14).

Conclusion : Recurrent rectal cancer and post-operative fibrosis can be distinguished from each other by analysis of proton MR spectroscopic features, and ^{1}H-MRS can be a new method for differential diagnosis between recurrent rectal cancer and post-operative fibrosis.

Index words : Magnetic resonance spectroscopy
Rectum, MR
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Local recurrence of carcinoma of the rectum and sigmoid colon after surgery is common, occurring in 20-55% of patients (1-5). Anastomotic recurrence occurs mostly after anterior resection and is usually related to residual tumor outside the colorectal wall that grows into the suture site. 80% of these recurrences develop within the first 2years, early and frequent follow-up studies are recommended (6). However, the differentiation of locally recurrent tumor from benign postoperative fibrosis may be difficult. Some studies have examined MR imaging is a sensitive method for detecting masses after colorectal surgery (1, 3, 7, 8), but it is not specific for recurrent tumor (3, 7, 9).

Localized in vivo proton magnetic resonance spectroscopy (^{1}H-MRS) has been shown to provide information about the contents of organic compounds in living tissues. To our knowledge, studies of human in vivo ^{1}H-magnetic resonance spectroscopy (^{1}H-MRS) for recurrent rectal cancer and postoperative fibrosis are none. Only one study reported in vivo ^{1}H-MRS feature of human rectal adenocarcinoma (10). We designed this study to know the differences of proton MR spectroscopic features between recurrent rectal cancer and postoperative fibrosis, and to evaluate the possibility to discriminate them by analyzing in vivo ^{1}H-MR spectra.

Materials and Methods

Subjects

Eleven patients (seven women, 4 men; mean age$\pm$ SD, 54 years$\pm$13; age range, 42-72 years), with recurrent rectal cancer and fourteen postoperative fibrosis (five women, 9 men; mean age$\pm$SD, 49 years $\pm$6; age range, 27-72 years) underwent proton MR spectroscopy at Inha University College of Medicine.

All of our subjects had adenocarcinoma at the rectum and underwent spiral CT for follow up after rectal surgery. All of our subjects were showed wall thickening in anastomosis site or presacral mass that could not definitely characterized as benign or malignant on spiral CT.

All subjects underwent biopsy for characterization of recurrence or not. Informed consents for ^{1}H-MRS were obtained from all patients and the study protocol was conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution' s human research committee.

MR spectroscopy

All MR spectroscopic examinations were performed with a 1.5-T whole-body system (MRI/MRS, version 5.5; GE Medical Systems, Milwaukee, Wis) equipped with actively shielded gradients. For all spectra, STEAM (stimulated echo acquisition method) localization sequence incorporated with three-pulse CHESS (chemical shift selective) sequence to suppress the water signal, was used with the following acquisition parameters: 3,000/30 (repetition time msec/echo time msec), 13.7-msec mixing time, 2,500-Hz sweep width, 2,048 data points, averaging no. = 128, and one number of examination (NEX).

In all patients, a localization voxel of 3.4 ($1.5\times1.5\times1.5$) cm^3 was placed in the safely within the soft tissue mass lesion in order to reduce contamination from adjacent normal fatty tissue. STEAM spectra were acquired in all subjects in the supine position. The subjects breathed in quiet regular respiration without respiratory interruption during signal acquisition.

Quantification of Metabolite Ratios

The post-processing procedure was carried out at a SUN SPARC 20 workstation (SUN Computer Inc.) with Spectral Analysis/General Electric (SA/GE) software incorporated with low frequency filtering of residual water signal removal, apodization by 0.5 Hz of exponential line broadening, zerofilling of 8k, Fourior transformation, and lorenzian to gaussian transformation according to the method described by Kreis et al. (11). Two authors (Y.S.J., S.G.C.,) analyzed the ^{1}H-MR spectroscopic signal intensities of various metabolites. We evaluated the spectra with an attention to the differences of pattern of the curves between recurrent rectal cancer and postoperative fibrosis.

MR Spectrum Analyses and Statistical Methods

^{1}H- MR spectra were analysed with particular attention to the presence of lipid peaks at 0.9-1.6 ppm, and a metabolite peak at 1.6-4.1 ppm. The ratio of peak area of all peaks at 1.6-4.1 ppm to lipid (0.9-1.6 ppm) was calculated in recurrent rectal cancer and postoperative fibrosis group, and compared the results between these two groups. We also evaluated the

sensitivity and specificity for discriminating recurrent rectal cancer from the postoperative fibrosis by analysis of ^{1}H-MRS. The chi-square test was used to analysis spectroscopic data, and difference rankings between means at a statistically significant level were thus established. P value of less than .05 was considered to indicate a statistically significant difference.

Results

Clinical characteristics of all subjects with recurrent rectal cancer and postoperative fibrosis are described in Table 1 and 2. In all cases, we successfully obtained ^{1}H-MR spectra of the thickened rectal wall within a voxel. The representative in vivo ^{1}H-MRS features for patients with recurrent rectal cancer and postoperative fibrosis are shown in Fig. 1 and 2. In subjects with recurrent rectal cancer, the largest peak on ^{1}H-MRS occurred at 0.9-1.6 ppm where the chemical shift of the lipid occurs (Fig. 1, 2). Also prominent peak on 1H-MRS occurred at 1.6-4.1 ppm where the chemical shift of the unknown metabolites.

The most significant difference in the ^{1}H-MRS features between recurrent rectal cancer and postoperative fibrosis was a difference in the lipid content. The ^{1}H-MR spectra of postoperative fibrosis showed significantly diminished amount of lipids as compared with those of recurrent rectal cancer. The ratio of P (1.6-4.1 ppm) / P (0.9-1.6 ppm) in recurrent rectal cancer was much lower than that in postoperative fibrosis with a statistical significance ($p < .05$) due to increased peak area of lipids. The ratio

Table 1. MRS of Recurrent Rectal Cancer

Number	Age	Sex	1.6-4.1 ppm	0.9-1.6 ppm	Ratio
1	54	F	66.035	205.224	0.32178
2	42	F	19.696	111.709	0.17631
3	68	M	69.049	128.780	0.53618
4	64	F	280.779	1854.880	0.15137
5	60	M	28.547	95.636	0.29850
6	71	M	27.327	77.040	0.35472
7	61	F	38.124	130.245	0.29271
8	59	M	40.125	148.326	0.27052
9	58	M	53.654	250.124	0.21451
10	65	M	70.352	177.264	0.39688
11	72	M	81.705	489.454	0.16693

Ratio : P (1.6-4.1 ppm) / P (0.9-1.6 ppm)

Table 2. MRS of Postoperative fibrosis

Number	Age	Sex	1.6-4.1ppm	0.9-1.6ppm	Ratio
1	72	F	19.210	13.542	1.41858
2	27	M	27.302	31.201	0.87503
3	68	M	63.982	12.504	5.11676
4	57	F	41.230	22.130	1.86308
5	56	M	15.246	6.874	2.21797
6	68	M	26.102	5.213	5.00659
7	61	M	31.254	7.256	4.30727
8	70	F	44.120	20.310	2.17225
9	57	M	24.123	13.486	1.78875
10	50	M	55.124	29.654	1.85893
11	51	M	81.394	35.991	2.26150
12	46	M	91.454	40.057	2.28306
13	63	F	65.124	12.842	5.07113
14	65	F	33.120	19.642	1.68620

Ratio : P (1.6 - 4.1 ppm) / P (0.9-1.6 ppm)

ranges of P (1.6-4.1 ppm) / P (0.9-1.6 ppm) in recurrent rectal cancer and postoperative fibrosis were 0.17 to 0.54 and 0.88 to 5.12, respectively. Mean (standard deviation of P (1.6-4.1 ppm) / P (0.9-1.6 ppm) in recurrent rectal cancer and postoperative fibrosis group were 0.29±0.11 and 2.71±1.48, respectively (Table 3). With a cut-off value of 0.6 for discriminating recurrent rectal cancer from postoperative fibrosis, both the sensitivity and specificity were 100%.

Discussion

Local recurrence of carcinoma of rectums develops in 20-55% of patients. MR imaging is a sensitive method for detecting masses after colorectal surgery, but its specificity is not better than that of CT (12). In these patients, benign and malignant processes cannot be distinguished on the basis of morphological appearance and signal intensity on MR images. Recent studies

Table 3. MRS of Mean Value

	Recurrent rectal cancer	Post-op. Fibrosis	P value
Mean±SD. of ratio	0.29±0.11	2.71±1.48	P < .05

SD : Standard deviation
Ratio : P (1.6-4.1 ppm) / P (0.9-1.6 ppm)

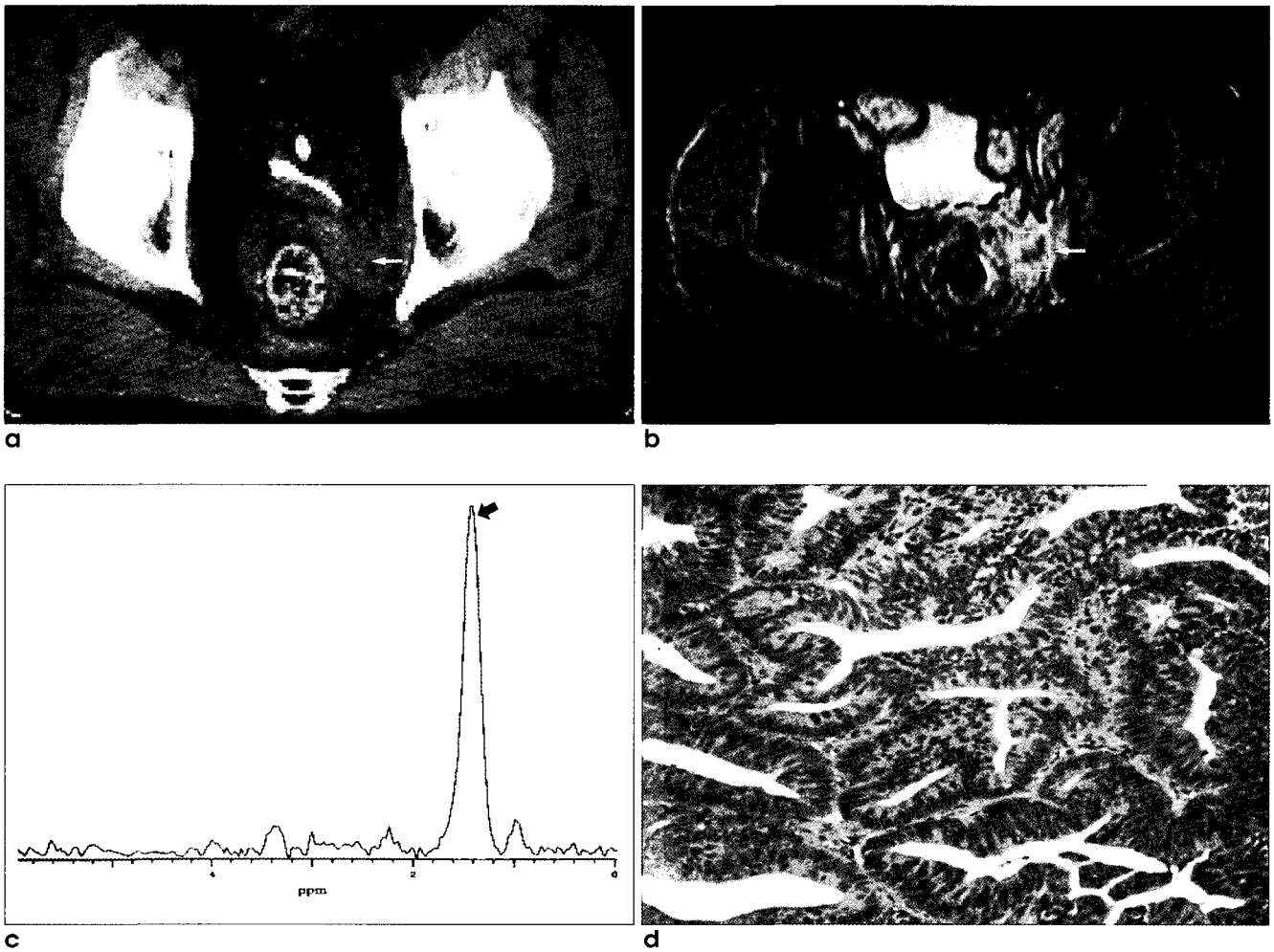

Fig. 1. Recurrent rectal cancer after low anterior resection. Post-enhance CT (**a**) and reference MR images (**b**) shows soft tissue mass (arrow) in perirectal area. Histopathology section (**c**) shows adenocarcinoma (H & E, original magnification, ×200). Prominent lipid peak (arrow) is seen in ^{1}H-MRS (**d**).

found that the signal intensities on T2 weighted images do not permit prediction of the histological diagnosis of a lesion (7). On T2 weighted images, high signal intensity was found in areas of viable tumor, tumor necrosis, benign inflammation, and edematous tissue (7). Also, low signal intensity was found in tumor-induced fibrosis and postoperative fibrotic tissue (7). Newer techniques, such as MR spectroscopy may hold the key to accurate distinction of recurrent rectal cancer from postoperative fibrosis.

The rapid proliferation of whole-body magnetic resonance imaging (MRI) magnets, with the potentials for MRS, radiologist and MR technicians have heightened interest in the development of MRS as a technique for clinical diagnosis. MRS is a powerful method that provides information on the biochemical status and physiological processes in vivo and is a qualitative as well as a quantitative method. Based on altered and/or specific metabolic profiles, including those of choline compounds and lipids, analytic ^{1}H-MRS has demonstrated its potential in the diagnosis and grading of colorectal adenocarcinoma (13-17). Furthermore, two-dimensional techniques have differentiated adenoma from carcinoma and determined cell line tumorigenicity based on cell surface fucosylation (18).

In the application of MRS to the abdominal organ, introducing noise into spectroscopic signals due to physiologic movement is a major obstacle in obtaining proper signals. Various methods for diminishing the introduced noise from physiologic movement, such as respiratory holding or patients' prone position during

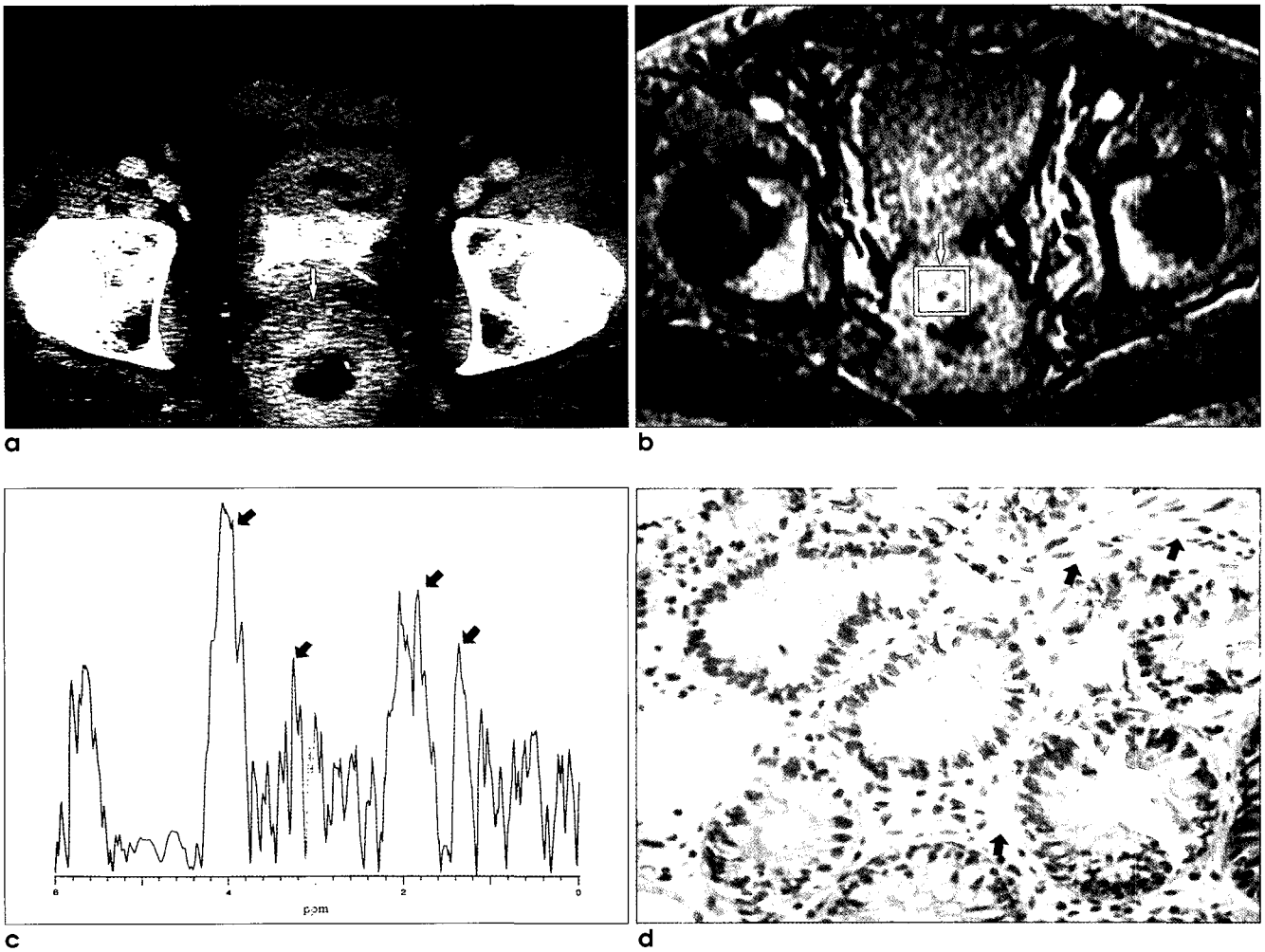

Fig. 2. Postoperative fibrosis after low anterior resection. Post-enhance CT (**a**) and reference MR images (**b**) shows wall thickening (arrow) and perirectal infiltration. C, Histopathology section (**c**) shows fibrosis (arrows) without malignant cell (H & E, original magnification, ×200). Multiple unknown prominent peaks (arrows) are seen in ^{1}H-MRS (**d**).

signal acquisition, were used in previous studies (19, 20). In our study, the in vivo ^{1}H-MR spectra were successfully obtained from the postoperative rectal mass in all subjects without respiratory interruption. We used a relatively long TR, which could enable patients to adapt their respiratory cycle to TR interval, so that the time of signal acquisition could fall approximately into maximal inspiration or expiration. Moreover, a small range of the postoperative rectum along the respiratory movement seemed to be helpful in diminishing noise.

Previous study reported that the most commonly detected metabolites were choline and lipid in locally advanced human rectal adenocarcinoma in vivo ^{1}H-MRS (10). This lipid resonance has previously been associated with necrosis and macrophage invasion, and is commonly associated with advanced clinical stage in colorectal and other malignancy (21). An elevated choline resonance is another well-recognized component of neoplastic tissue (22). But there are also significant unidentified metabolite peaks in locally advanced human rectal adenocarcinoma in vivo ^{1}H-MRS (10). A great variety is in expressed metabolites on ^{1}H-MRS from any organ and the precise identification of innumerable unknown peaks on the ^{1}H-MR spectra acquired in a commercial low field strength MR machine is nearly impossible. So, the development of simplified standardizing method for analysis of ^{1}H-MR spectra is necessary for extending clinical application of ^{1}H-MRS. In our study, we used the ratio between known and unknown peaks (i.e., lipid and other metabolite peaks).

The fibrosis and scarring are major morphologic change of benign postoperative fibrosis. Some level of restitution or restoration of the epithelium with various degrees of replacement of that tissue characterizes these changes by fibrous connective tissue or scar (23). The cellularity of the wound from cells including macrophage, inflammatory cells, myofibroblast, fibroblasts, and accumulation of type I collagen and the formation of a definitive scar composed dense collagen scar (23). In our study, ^{1}H-MR spectra of postoperative fibrosis showed significantly diminished amount of lipids as compared with that of recurrent rectal cancer. This result could be explained by much more fibrotic change of epithelial tissue in postoperative fibrosis. The ratio of P (1.6–4.1 ppm) / P (0.9–1.6 ppm) in recurrent rectal cancer was much higher than that in postoperative fibrosis with a statistical significance ($p < .05$) due to increased peak area of lipids, as previous study reported that lipid peak is prominent in locally advanced human rectal adenocarcinoma in vivo ^{1}H - MRS (10). We simply used the ratio between known lipid peaks and unknown metabolite peaks. Minute identification or specification of individual metabolic peak was not necessary in that analytic method. We could easily analyze and compare the ^{1}H-MR spectra of postoperative recturm using that method, and differentiation between recurrent rectal cancer and postoperative fibrosis was achieved by simple comparing that ratio between the two different groups.

This study has some limitations. First, the patient population in this study is relatively small. Second, respiratory movement and normal peristalsis can prevent adequate signal acquisition owing to the inconstant position of a voxel. If the voxel is contaminated with perirectal fat due to patients' physiologic motion or peristalsis, it may hard to know the real change of lipid contents within the lesion. However, postoperative rectum is relatively fixed organ, and we carefully located the voxel within the lesion. In our study, several peaks from unknown source also were demonstrated on the spectrum. Thus, further investigations with metabolic extracts with use of a solution nuclear MR spectroscopic method are needed to disclose the peaks of unknown sources.

In conclusion, this report is first study of in vivo ^{1}H-MRS in recurrent rectal cancer and postoperative fibrosis. Recurrent rectal cancer and postoperative fibrosis can be distinguished from each other by analysis of proton MR spectroscopic features and ^{1}H-MRS can be a new method for differential diagnosis between recurrent rectal cancer and postoperative fibrosis.

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재발성 직장암과 수술 후 섬유화의 감별 진단: 수소 MRS에 의한 예비보고

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목적 : 직장암 수술 후 재발성 직장암과 수술 후 섬유화의 수소 MRS의 소견의 차이가 있는지 알아보고, 수소 MRS를 이용하여 두 질환의 감별이 가능한지 분석하고자 하였다.

대상 및 방법 : 직장암 수술 후 직장 주위에 종괴를 보인 25명을 대상으로 수소 MRS를 분석하였다. 이중 11예는 재발성 직장암이고 14예는 수술 후 섬유화 였다. 모든 대상은 생검을 통하여 확진 하였다. 두 군의 수소 MRS의 그래프의 스펙트럼이 어떤 모양으로 다른지 분석하였다. 두 군에서의 1.6-4.1 ppm 대 lipid (0.9-1.6 ppm) [P (1.6-4.1 ppm)/P (0.9-1.6 ppm)]의 비율을 각각 계산하였고, 두 군의 결과의 차이를 비교하였다. 또한 수소 MRS에 의한 이 비율을 이용하여 두 군의 감별에 대한 민감도와 특이도를 분석하였다.

결과 : 수술 후 섬유화 군에서의 지방의 양이 재발성 직장암 군보다 통계적으로 유의하게 감소되었다. 1.6-4.1 ppm / 0.9-1.6ppm의 비율이 수술 후 섬유화 군에서 lipid peak의 감소로 인해 직장암 군보다 통계적으로 유의하게 높았으며 두 값의 평균 및 표준 편차는 각각 2.71±1.48과 0.29±0.11이였다. 두 군의 감별에서 결정 수치를 0.6으로 하였을 때 민감도와 특이도가 각각 100% 였다 (11/11, 14/14).

결론 : 재발성 직장암과 수술 후 섬유화는 수소 MRS 소견 분석으로 구별이 되며, 수소 MRS는 두 군의 감별진단에 새로운 방법이 될 수 있을 것으로 사료된다.

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