^{166}Ho-chitosan 복합체의 복강 내 투여를 위한 베타선 흡수선량 평가

원자력병원 싸이클로트론응용연구실[1], 핵의학과[2], 한국원자력연구소[3] 동위원소연구실

김은희[1] · 임상무[2] · 박경배[3]

= Abstract =

Beta Dosimetry in Intraperitoneal Administration of ^{166}Ho-chitosan Complex

Eun-Hee Kim, Ph.D.*, **Sang-Moo Lim**, M.D.† and **Kyung-Bae Park**, Ph.D.†

Cyclotron Application Laboratory, Department of Nuclear Medicine †, Korea Cancer Center Hospital, Seoul, Korea*
Department of Radioisotope †, Korea Atomic Energy Research Institute, Daejon, Korea

Intraperitoneal administration of radioisotopes is suggested to treat the metastatic ovarian cancer in the peritoneal cavity. Administering beta-emitting radioisotopes into the peritoneal cavity allows the maximum energy delivery to the cancerous cells of the peritoneal wall surface while sparing the normal cells located in deep site of the peritoneal wall. In this study, dose estimates of the peritoneal wall are provided to be used for prescribing the amount of ^{166}Ho-chitosan complex administered.

The ^{166}Ho-chitosan complex diffused in the peritoneal fluid may attach to the peritoneal wall surface. The attachment fraction of ^{166}Ho-chitosan complex to the peritoneal wall surface is obtained by simulating the ascites with Fischer rats. Both volume source in the peritoneal fluid and the surface source over the peritoneal wall surface are counted for the contribution to the peritoneal wall dose. The Monte Carlo code EGS4 is used to simulate the energy transfer of the beta particles emitted from ^{166}Ho. A plane geometrical model of semi-infinite volume describes the peritoneal cavity and the peritoneal wall. A semi-infinite plane of 10 μm in thickness at every 1 mm of depth in the peritoneal wall is taken as the target in dose estimation.

Greater than 98 percents of attachment fraction has been observed from the experiments with Fischer rats. Given 1.3 μCi/cm^2 and 2.4 μCi/ml of uniform activity density, absorbed dose is 123 Gy, 8.59 Gy, 3.00 Gy, 1.03 Gy, and .327 Gy at 0 mm, 1 mm, 2 mm, 3 mm, and 4 mm in depth to the peritoneal wall, respectively. **(Korean J Nucl Med 1998;32:99-108)**

Key Words: Intracavitary radiation therapy, beta dosimetry, ^{166}Ho-chitosan complex

책임저자: 김은희, 서울시 노원구 공릉동 215-4
Tel: (02) 970-1353, Fax: (02) 975-3231, E-mail: ekim@kcchsun.kcch.re.kr

Introduction

Ovarian cancer is one of the highest causes of mortality among gynecologic cancers. The malignancy originates in the ovaries and is generally detected when it has metastasized to the surface of the peritoneum. The peritoneal cavity is a space defined by the mesothelial lining which surrounds various organs in the abdominal cavity. This lining, called peritoneum, covers the entire abdominal wall of the body from the diaphragm to the pelvic floor. The cavity lining has a highly variable thickness. Normally, the cavity contains a very slight amount of watery fluid which tends to lubricate its inner surface. In pathologic conditions, however, the cavity may become greatly distended with fluid.

The conventional treatment of the ovarian cancer involves surgical debulking of the primary tumor, followed by a regimen of chemotherapy and/or radiation therapy to the regions at risk for spread[1,2]. The diffuse nature of peritoneal disease requires the treatment of the entire abdomen. In radiation therapy for treating ovarian metastases, ^{198}Au colloids[3] and radioactive chromic phosphate (^{32}P colloids)[4,5] have been administered directly into the peritoneal cavity to augment the dose to the peritoneal surface.

Intracavitary radiation therapy with Holmium-166 chitosan complex is considered to be a strong candidate protocol for treating ovarian metastases to the peritoneum. ^{166}Ho has nuclear characteristics ideal for therapeutic use: (1) beta-particle emissions of 99% yield with the endpoint energy of 1.855 MeV, which corresponds to 9 mm of CSDA (continuous slowing down approximation) range in liquid water, (2) half-life of 26.9 hours, and (3) 81-keV γ-rays of 5.4% yield, which is useful for detection. Chitosan is almost non-toxic, antigenically inactive, biocompatible, and biodegradable in animal, and therefore it is suitable for biomedical and pharmaceutical applications. The interest of chitosan in research is even more enhanced by the possibility of polycationic chelating and the ready solubility in dilute acetic acid.

^{166}Ho is readily produced from ^{165}Ho, whose natural abundance is 100%, by ^{165}Ho(n,γ)^{166}Ho reaction. The 30-MW research reactor HANARO in Korea Atomic Energy Research Institute(KAERI) is available for neutron irradiation. Holmium-166 chitosan complex, or ^{166}Ho-CHICO, can be produced with high labeling yield(>99%) by mixing acidic chitosan solution with ^{166}Ho(NO_3) solution at room temperature[6]. The autoradiography performed after injecting ^{166}Ho-CHICO into a lesion has shown that ^{166}Ho-CHICO is well confined within the lesion.

The ^{166}Ho-CHICO can be injected into the peritoneal cavity distended with fluid. ^{166}Ho-CHICO inside the peritoneal cavity emits beta particles, which deliver energy both to the peritoneal fluid and to the peritoneal wall. When ^{166}Ho-CHICO is injected into the peritoneal cavity, it may be distributed over the peritoneal wall or in the peritoneal fluid. To estimate the dose to the peritoneal wall, the source activity both over the peritoneal wall surface and in the peritoneal fluid should be known. The largest value found in the literature for peritoneal cavity volume is 4000 cm[37], and measured values of the peritoneum thickness in adults range from 0.5 to 2 mm with an average of 1 to 1.5 mm[8].

In this study, dose to the peritoneal wall delivered by intraperitoneal injection of ^{166}Ho-CHICO is estimated by Monte Carlo simulation. To find the degree that ^{166}Ho-CHICO is bound to the peritoneal wall surface, ^{166}Ho-CHICO is injected into Fischer rats in a pathologic condition of peritoneal cavity. The volume of the peritoneal cavity is assessed by using ^{99m}Tc-HSA. Among the adminis-

tered ^{166}Ho-CHICO, the fraction that is diffused in the peritoneal fluid is found by extracting some peritoneal fluid, counting the ^{166}Ho activity density, and multiplying it by the known volume of the peritoneal cavity. The remaining of the ^{166}Ho-CHICO administered is considered to be bound to the peritoneal wall surface. Both volume and surface sources of ^{166}Ho are considered in estimating dose to the peritoneal wall.

Methods

The whole body autoradiography of a mouse intraperitoneally administered with ^{166}Ho-CHICO is performed to see whether ^{166}Ho-CHICO is confined within the peritoneal cavity.

1. Measurement of the Peritoneal Cavity Volume

The procedure of measuring the peritoneal cavity volume is demonstrated with Fischer rats. Normal saline is infused into the peritoneal cavity of Fischer rats, which simulates the pathologic condition of the peritoneal cavity. The procedure is as follows:

1) Inject 30 ml of normal saline (0.9% NaCl solution) into the peritoneal cavity of a Fischer rat.
2) Measure the weight of the rat.
3) Infuse 100 μCi/0.5 ml of ^{99m}Tc-HAS into the peritoneal cavity of the rat.
4) Extract 0.5 ml of peritoneal fluid.
5) Sacrifice the rat.
6) Open the abdomen of the rat and spill out the peritoneal fluid.
7) Measure the weight of the rat.
8) Cut out part of the peritoneal wall.
9) Count the gamma-ray emissions from the extracted peritoneal fluid.

The volume of the peritoneal fluid is obtained by dividing the total ^{99m}Tc activity administered by the volume activity density of ^{99m}Tc counted in step 9. The weight difference of the rat before (step 2) and after (step 7) sacrifice also informs the volume of the peritoneal fluid.

2. Measurement of the Source activity of ^{166}Ho

1) Inject 10 ml of normal saline (0.9% NaCl solution) into the peritoneal cavity of a Fischer rat.
2) Inject 1 mCi/ml of ^{166}Ho-CHICO into the peritoneal cavity of the rat.
3) On the next day, inject 30 ml of normal saline (0.9% NaCl solution) into the peritoneal cavity of the rat.
4) Measure the weight of the rat.
5) Extract 0.5 ml of peritoneal fluid.
6) Inject 100 μCi/0.5 ml of ^{99m}Tc-HAS into the peritoneal cavity of the rat.
7) Extract 0.5 ml of peritoneal fluid.
8) Open the abdomen of the rat and spill out the peritoneal fluid.
9) Measure the weight of the rat.
10) Cut out part of the peritoneal wall.
11) Perform gamma counting in ^{99m}Tc range with the peritoneal fluid extracted in step 7.
12) Perform gamma counting in ^{166}Ho range with the peritoneal fluid extracted in step 5.
13) Perform the autoradiography with the cut sample of peritoneal wall.
14) Perform gamma counting with the peritoneal wall sample of unit area.

10 ml of normal saline injected in step 1 is considered to be absorbed into the body fluid in a day, leaving ^{166}Ho-CHICO inside the peritoneal cavity. The volume of the peritoneal fluid is measured by dividing the total ^{99m}Tc activity injected in step 6 by the volume activity density of ^{99m}Tc

counted in step 11. The volume of the peritoneal fluid is obtained also from the weight difference measured in steps 4 and 9. The fraction of the administered ^{166}Ho-CHICO that is diffused in the peritoneal fluid is obtained by multiplying the volume activity density of ^{166}Ho counted in step 12 by the known volume of the peritoneal fluid. Subtracting this ^{166}Ho activity from the initial ^{166}Ho activity administered in step 2 results in the activity that is distributed over the peritoneal wall surface. The autoradiography performed in step 13 is to show the pattern of ^{166}Ho distribution over the peritoneal wall surface.

The volume activity density ^{166}Ho is given in step 12. On the assumption that the areal activity density of ^{166}Ho is uniform over the peritoneal wall surface, calculating the areal activity density requires the surface area of the peritoneal wall to be known. If a nominal value of the peritoneal wall surface area for Fischer rats was available, the areal activity density would be calculated by dividing the ^{166}Ho activity distributed over the peritoneal wall surface by its area. In this study, the areal activity density of ^{166}Ho over the peritoneal wall surface is taken from the gamma counting per unit peritoneal wall in step 14.

3. Correction for the Interference of ^{166}Ho Gamma Count to the ^{99m}Tc Gamma Count and vice versa

The NaI(Tl) scintillation counter is used to estimate the activity in a sample by counting the gamma-rays emitted from the sample. In real clinical applications, the volume of the peritoneal cavity would be measured by infusing ^{99m}Tc-HAS into the peritoneal fluid in a situation that ^{166}Ho-CHICO is already diffused in the peritoneal fluid. The close gamma-ray energy peaks of ^{166}Ho (81 keV) and ^{99m}Tc (140 keV) can cause an error in count. Since the half-life of ^{99m}Tc is short (6 hours) as compared to that of ^{166}Ho (26.9 hours) and the activity of the infused ^{99m}Tc-HAS is relatively low, the interference of ^{99m}Tc gamma emissions to ^{166}Ho gamma count can be minimized by performing the ^{166}Ho gamma counting in a time lapse long enough for ^{99m}Tc in a sample to decay to a negligible activity level. In terms of the error in ^{99m}Tc gamma count, the low gamma emission yield (5.4%) of ^{166}Ho as compared to that (90%) of ^{99m}Tc would result in a negligible influence on ^{99m}Tc gamma count. To find the degree of the overestimation in ^{99m}Tc gamma count due to ^{166}Ho contamination or in ^{166}Ho gamma count due to ^{99m}Tc contamination, gamma counting is performed for samples with ^{166}Ho of a constant activity added with ^{99m}Tc of a varying activity.

4. EGS4 Simulation

Transport in liquid water of beta particles emitted from ^{166}Ho is traced using the Monte Carlo code EGS4[9]. The tracing cutoff energy is set at 1 keV for photons and 10 keV for electrons. As shown in Fig. 1, a semi-infinite volume represents the peritoneal cavity filled with fluid and the other side represents the peritoneal wall. A 10 μm-thick infinite plane is defined as a target volume being located every 1 mm, from 0 mm to 4 mm, in depth toward the peritoneal wall. Considering that the range in the liquid water of 10 keV-electrons is 2.6 μm, the plane target is thick enough to enclose the local energy depositions.

Dose to the peritoneal wall is attributed to both the ^{166}Ho-CHICO bound to the peritoneal wall surface and that diffused in the peritoneal fluid. The surface source and the volume source are assumed to be uniformly distributed over the surface of the peritoneal wall and in the peritoneal fluid, respectively.

Results

The whole body autoradiograph of a mouse administered with ^{166}Ho-CHICO has shown that ^{166}Ho-CHICO is confined within the peritoneal cavity(see Fig. 2). The values of peritoneal fluid volume calculated using the ^{99m}Tc gamma count have ranged from 31.3 ml to 34.6 ml while the weight differences measured before and after sacrifice of Fischer rats have ranged from 21.3 ml to 23.4 ml. For 30 ml of normal saline injected to simulate the peritoneal fluid, the calculational approach using ^{99m}Tc gamma count has led to overestimation while measuring the weight difference has led to underestimation. The overestimation using ^{99m}Tc gamma count suggests that part of ^{99m}Tc-HAS injected might have been attached to

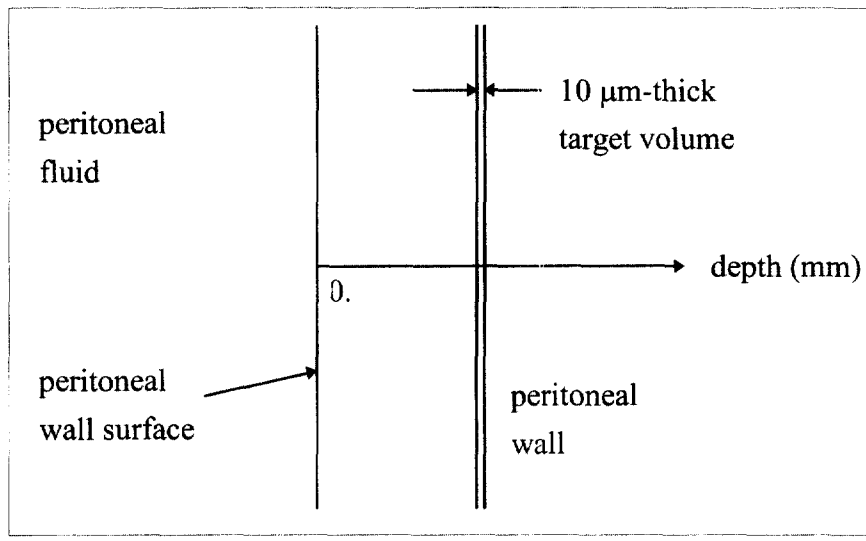

Fig. 1. Geometrical model for calculating dose to the peritoneal wall.

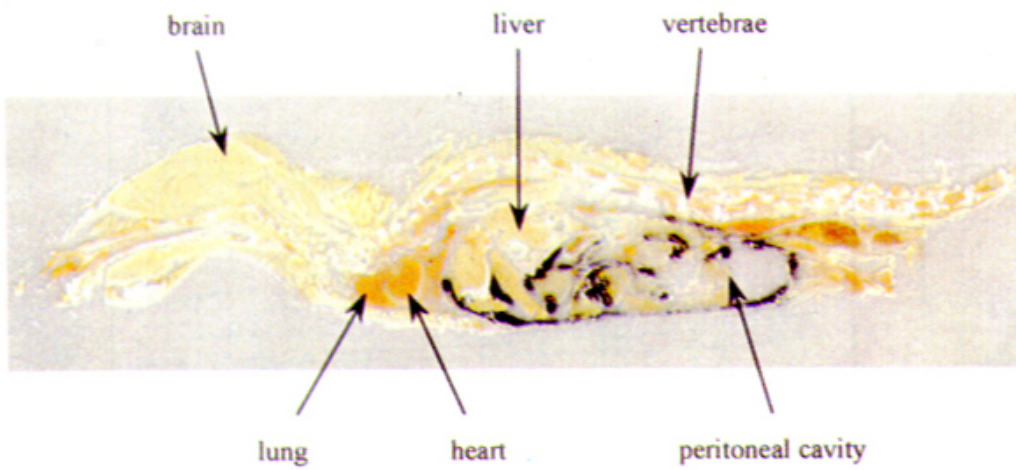

Fig. 2. The whole body autoradiograph of a mouse intraperitoneally injected with ^{166}Ho-CHICO, which is infused with a section of the mouse prepared using an auto-cryotome.

the peritoneal wall surface. The underestimation in the weight difference implies that spilling the peritoneal fluid might have been incomplete.

The binding fraction of ^{166}Ho-CHICO to the peritoneal wall surface has been obtained at over 98%. The distribution of ^{166}Ho-CHICO over the peritoneal wall surface has been observed by autoradiography. The autoradiograph has shown a rather uniform distribution of ^{166}Ho-CHICO in overall, but still showing local non-uniformity (see

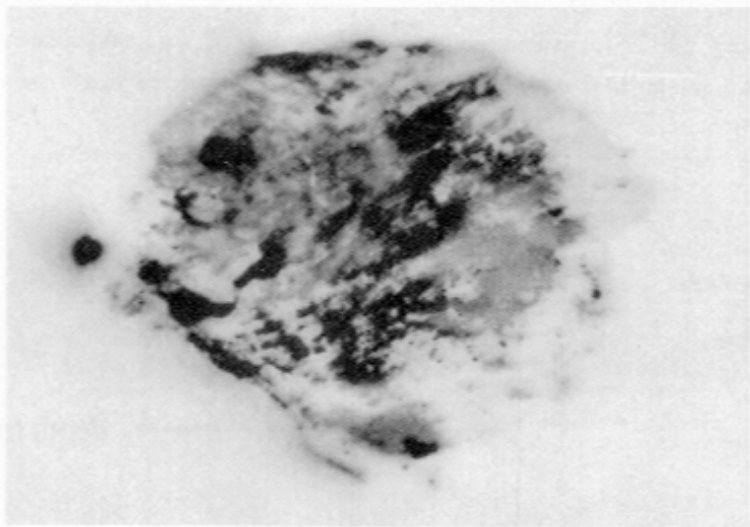

Fig. 3. Autoradiograph of a piece of the peritoneal wall of the Fischer rat injected with ^{166}Ho-CHICO.

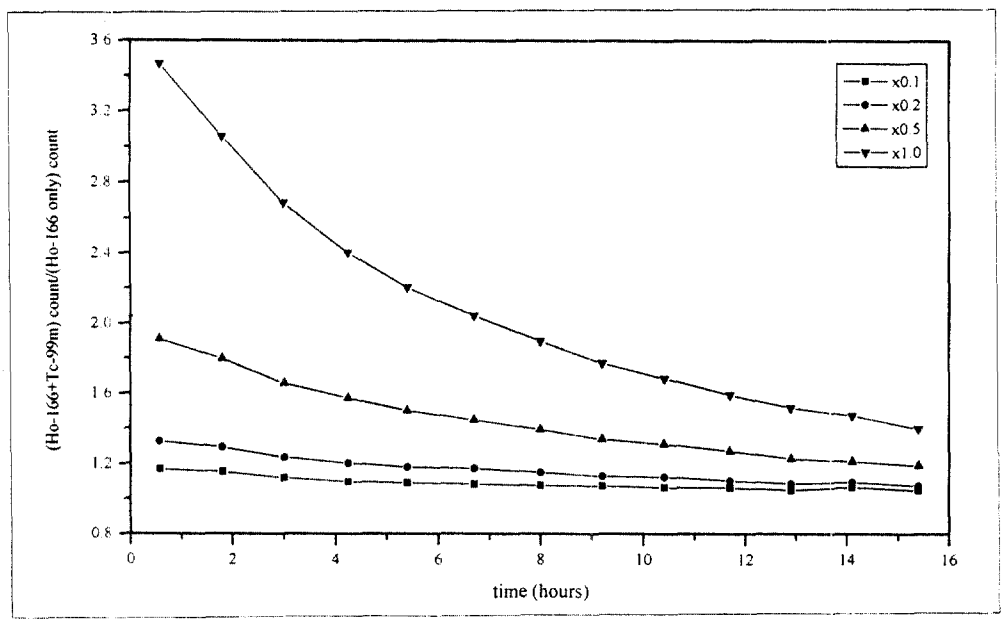

Fig. 4. Gamma count ratio of ^{166}Ho sample contaminated with ^{99m}Tc to pure ^{166}Ho sample. The initial relative activity of ^{99m}Tc to pure ^{166}Ho is 0.1, 0.2, 0.5 or 1.0.

Fig. 3).

The mutual interference of ^{166}Ho and ^{99m}Tc in gamma count has been tested with samples of a varying ratio of ^{99m}Tc to ^{166}Ho activity. Fig. 4 displays the ratio of gamma count in ^{166}Ho range from a ^{166}Ho source added with ^{99m}Tc to that from the pure ^{166}Ho source. Greater contamination activity of ^{99m}Tc results in higher degree of overestimation in gamma count for ^{166}Ho. The shorter half-life of ^{99m}Tc (6 hours) as compared to that of ^{166}Ho (26.9 hours) has led to a lower degree in overestimation as decay proceeds. Displayed in Fig. 5 is the ratio of gamma count in ^{99m}Tc range from a ^{99m}Tc source added with ^{166}Ho to that from the pure ^{99m}Tc source. Greater contamination activity of ^{166}Ho results in higher degree of overestimation in gamma count for ^{99m}Tc. Due to longer half-life of ^{166}Ho (2.69 hours) as compared to that of ^{99m}Tc (6 hours), the contamination ratio of ^{166}Ho activity increases as decay proceeds. Therefore, a greater overestimation of ^{99m}Tc gamma count is observed. Theoretically, the ratio should not be lower than 1.0. The data of less than 1.0 in Fig. 5 can be explained by the negligible interference of ^{166}Ho to the gamma count in ^{99m}Tc range and the statistical error in count itself. In Fig. 4 and 5, the numbers in legends are the ratios in activity of the contaminant to the pure object of interest.

Table 1. Electron Dose to a 10 μm-thick Target at a Varying Depth into the Peritoneal Wall for ^{166}Ho of 1 μCi/cm^2 in Initial Activity Density over the Peritoneal Wall Surface

Target depth(mm)	Absorbed dose(Gy)	Relative absorbed dose[a]	Percent cumulative energy absorption[b]
0	80.8(6.10%)[c]	100	-
1	3.91(5.99%)	4.84	92.5
2	1.09(5.31%)	1.35	98.0
3	0.329(6.38%)	0.408	99.5
4	0.0939(7.25%)	0.116	100

a. absorbed dose value relative to that at the peritoneal wall surface

b. percent energy abosrption within the target depth; energy absorbed within 4 mm in depth is normalized to 100%

c. percent fractional standard deviation

Table 2. Electron Dose to a 10 μm-thick Target at a Varying Depth into the Peritoneal Wall for ^{166}Ho of 1 μCi/ml in Initial Activity Density in the Peritoneal Fluid

Target depth(mm)	Absorbed dose(Gy)	Relative absorbed dose[a]	Percent cumulative energy absorption[b]
0	7.40(8.24%)[c]	100	-
1	1.46(6.56%)	19.7	72.5
2	0.658(6.09%)	8.89	89.8
3	0.252(5.57%)	3.40	97.2
4	0.0855(3.13%)	1.16	100

a. absorbed dose value relative to that at the peritoneal wall surface

b. percent energy abosrption within the target depth; energy absorbed within 4 mm in depth is normalized to 100%

c. percent fractional standard deviation

Dose to the peritoneal wall due to surface source is presented in Table 1. For 1 μCi/cm^2 of areal activity density on the peritoneal wall surface, dose to the peritoneal wall is 80.8 Gy, 3.91 Gy, 1.09 Gy, 0.329 Gy, and 0.0939 Gy at 0 mm, 1 mm, 2 mm, 3 mm, and 4 mm in depth toward the peritoneal wall, respectively. Dose to the peritoneal wall due to volume source is presented in Table 2. For 1 μCi/ml of volume activity density in the peritoneal fluid, dose to the peritoneal wall is 7.40 Gy, 1.46 Gy, 0.658 Gy, 0.152 Gy, and 0.0855 Gy at 0 mm, 1 mm, 2 mm, 3 mm, and 4 mm in depth toward the peritoneal wall, respectively.

For the surface source, dose to the peritoneal

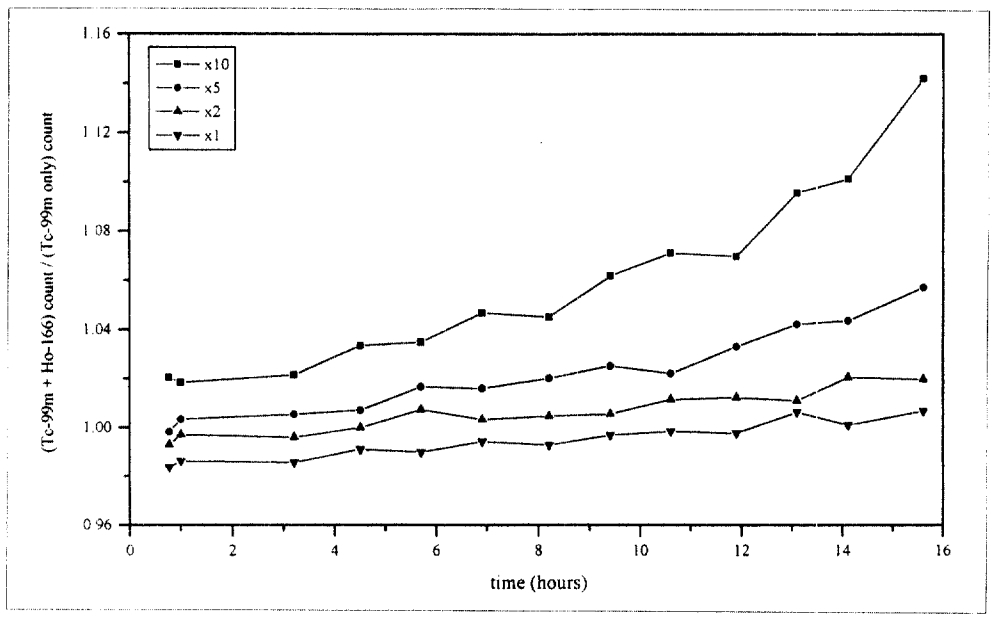

Fig. 5. Gamma count ratio of ^{99m}Tc sample contaminated with ^{166}Ho to pure ^{99m}Tc sample. The initial relative activity of ^{166}Ho to pure ^{99m}Tc is 1, 2, 5 or 10.

Table 3. Electron Dose to a 10 μm-thick Target at a Varying Depth into the Peritoneal Wall for ^{166}Ho of 1.3 μCi/cm^2 and 2.4 μCi/ml in Initial Activity Density over the Peritoneal Wall Surface and in the Peritoneal Fluid, respectively

Target depth(mm)	Absorbed due to ^{166}Ho on the peritoneal wall surface[a]	absorbed dose due to ^{166}Ho in the peritoneal fluid[b]	Total absorbed dose
0	105.(85%)[c]	17.8(15%)	123
1	5.08(59%)	3.50(31%)	8.59
2	1.42(46%)	1.58(54%)	3.00
3	.428(41%)	.605(59%)	1.03
4	.122(31%)	.205(69%)	.327

a. 1.3×(data in Table 1)

b. 2.4×(data in Table 2)

c. percent of the total absorbed dose

wall at 3 mm in depth is reduced to less than 1 % of that at the peritoneal wall surface. On the other hand, volume source results in more gradual reduction in dose as the target moves toward the peritoneal wall. The dose at 4 mm in depth is still greater than 1 % of that at the peritoneal surface. For the surface source, more than 90 % of the total energy absorption within 4 mm in depth attributes to the energy absorption within 1 mm in depth. For the volume source, on the other hand, the energy absorption within 1 mm in depth accounts for about 72.5 % of the total energy absorption within 4 mm in depth.

Dose estimates for standard activity density(1 μCi/cm^2 and 1 μCi/ml) have been applied to one experimental case. With 1.3 μCi/cm^2 of volume activity density in the peritoneal fluid and 2.4 μCi/ml of areal activity density over the peritoneal wall surface, dose to the peritoneal wall is 123 Gy, 8.59 Gy, 3.00 Gy, 1.03 Gy, and 0.327 Gy at 0 mm, 1 mm, 2 mm, 3 mm, and 4 mm in depth, respectively (see Table 3). The major contribution comes from the surface source for target volume close to the peritoneal surface while it does from the volume source for target volume at a greater depth.

Discussion

Dose to the peritoneal wall attributes to both the surface source attached to the peritoneal wall surface and the volume source distributed in the peritoneal fluid. Dose estimation for the experimental case has been performed assuming the uniformity in ^{166}Ho-CHICO distribution for both the volume source and the surface source. The assumption of uniformity in volume source distribution is quite reasonable. The uniformity in surface source distribution, however, may not be always the case. Autoradiographs of peritoneal wall samples have restrictions in terms of representing the condition over the whole peritoneal wall surface. Nevertheless, the uniform distribution of the surface source is the assumption of choice at this moment.

Summary

^{166}Ho-chitosan complex, or ^{166}Ho-CHICO, is a candidate pharmaceutical for intracavitary radiation therapy of ovarian metastases. ^{166}Ho-CHICO is well confined within the peritoneal cavity, not contaminating the outside. Beta particles emitted from ^{166}Ho deliver energy to the peritoneal wall with high LET. At the same time, their short range spares the outside normal tissue.

It has been shown that the volume of the peritoneal fluid measured by using ^{99m}Tc-HSA meets the actual value within a small error range. With the binding fraction of ^{166}Ho-CHICO to the peritoneal wall surface known and given the amount of activity administered, the areal activity density over the peritoneal wall surface and the volume activity density in the peritoneal fluid can be calculated for a varying volume of the peritoneal cavity in pathologic condition. Using the estimates of dose to the peritoneal wall for standard areal and volume activity density, the amount of ^{166}Ho-CHICO to be administered can be suggested for a varying goal dose to the peritoneal wall.

Acknowledgment

The authors acknowledge Wui-Sup Chung and Kwang-Sun Woo for their work.

References

1) Fuks Z, Yahalom J, Brenner H: The treatment of

carcinoma of the ovary in radiation therapy of gynecologic cancers. *Alan R. Liss, New York,* 1987.

2) Horyon J and CaputoT: Gynecologic cancer in clinical oncology. *Saunders WB, New York,* 1977.
3) Andrews A, Root S, Kerman HD, Bigelow RR: Intracavitary colloidal radiogold in the treatment of effusion caused by malignant neoplasm. *Ann. Surg.* 1953;137:375-381.
4) Boye E, Lindegoard MW, Paus E, Skretting A., Davy M, Jakobsen E: Whole-body distribution of radioactivity after intraperitoneal administration of P-32 colloids. *Br. J. Radiol.* 1984;57:395-402.
5) Currie JL, Bagne F, Harris C, Sullivan DL, Surwit EA, Wilkinson RH, Creasman WT: Radioactive chromic phosphate suspension: studies on distribution, dose absorption and effective therapeutic radiation in phantoms, dogs and patients. *Gynecol. Oncol.* 1981;12:19-218.
6) Park KB, Kim YM. Shin BC, Kim JR: Study on the preparations of new ^{166}Ho-chitosan complex and its macroaggregates for a potential use of internal radiotherapy. *The Korean J. of Nucl. Med.* 1996;30(3):351-160.
7) Walton R, Sinclair W: Intracavitary irradiation with radioactive colloidal gold in the palliative treatment of malignant pleural and peritoneal effusions. *Br. Med. Bull.* 1952;8:165-171.
8) Watson EE, Stabin MG, Davis JL, Eckerman KF: A model of the peritoneal cavity for 1use in internal dosimetry. *J. Nucl. Med.* 1989;30:2002-2011.
9) Rosenshein N, Blake D, McIntyre P, Parmley T, Natarajan TK, Dvornicky J, Nickoloff E: The effect of volume on the distribution of substances instilled into the peritoneal cavity. *Gynecol. Oncol.* 1978;6:106-110.