大韓核醫學會誌 : 第31卷 第4號 1997

Beta Dosimetry for Applying ^{166}Ho-chitosan Complex to Cystic Brain Tumor Treatment : Monte Carlo Simulations Using a Spherical Model

Cyclotron Application Laboratory[1], Department of Neurosurgery[2], Department of Nuclear Medicine[3], Korea Cancer Center Hospital, Seoul, Korea
Department of Radioisotope[4], Korea Atomic Energy Research Institute, Daejon, Korea

Eun-Hee Kim, Ph.D.[1], Chang-Hun Rhee, M.D.[2], Sang-Moo Lim, M.D.[3] and Kyung-Bae Park, Ph.D.[4]

= 국문 초록 =

^{166}Ho-chitosan 복합체를 이용한 낭성뇌종양 치료를 위한 베타선의 흡수선량 평가 : 구형 모델을 이용한 Monte Calro 모사계산

한국원자력병원 싸이클로트론응용연구실[1], 신경외과[2], 핵의학과[3], 한국원자력연구소 동위원소연구실[4]

김은희[1] · 이창훈[2] · 임상무[3] · 박경배[4]

낭성뇌종양은 낭 내부에 베타선을 방출하는 방사성동위원소를 주입하여 낭 내부 및 낭벽에 존재하는 암세포에 일정량의 방사선 에너지를 전달함으로써 그 치료 효과를 기대할 수 있다. 본 연구에서는 ^{166}Ho-chitosan 복합체를 낭성뇌종양 치료에 이용하고자 할 때 낭의 크기와 주입되는 방사능의 변화에 따라 낭벽에 전달되는 방사선 흡수선량이 어떻게 변화하는가를 평가하고자 한다.

구형의 종양성 낭 모델에 대하여 Monte Carlo code인 EGS4를 이용하여 ^{166}Ho 베타선의 에너지 전달 현상에 대한 모사계산을 수행한다. 종양성 낭 내부에 주입된 ^{166}Ho-chitosan 복합체의 낭내 분포는 낭 내부액과 섞여있거나 낭벽 표면에 부착되는 두 가지 경우를 고려한다. 방사선 조사의 표적 영역으로서, 낭벽의 표면으로부터 매 1mm 깊이의 체적을 설정하여 4mm 깊이까지 고려한다. 직경이 각 1cm, 2cm, 그리고 3cm 인 종양성 낭을 평가 대상으로 설정한다.

직경이 3cm인 종양성 낭에 10mCi의 ^{166}Ho-chitosan 복합체가 주입되어 낭 내부에 균일하게 분포하였다고 가정하였을 경우에 1mm 두께의 낭벽에 전달되는 방사선 흡수선량은 매 1mm 깊이의 낭벽 체적에서 각각 40.06Gy, 14.96Gy, 5.315Gy, 1.660Gy으로 계산되었다. 한편, 낭 내부에 주입된 10mCi의 ^{166}Ho-chitosan 복합체가 낭벽에 균일하게 분포하였다고 가정하였을 경우에는 매 1mm 두께의 낭벽 체적에 전달되는 방사선 흡수선량이 601.7Gy, 188.7Gy, 73.87Gy, 27.80Gy로 평가되었다. 낭 내부에 주입된 ^{166}Ho-chitosan 복합체가 낭벽에 부착될 가능성이 있음이 한 임상 적용 예에서 시사된 바, 정확한 ^{166}Ho-chitosan 복합체의 낭 내부벽 부착률을 확인함으로써 낭벽에 대한 흡수선량을 예측하고 이를 근거로 주입할 ^{166}Ho-chitosan 복합체의 양을 결정해야 할 것이다.

Key Words : Cystic brain tumor, beta dosimetry, ^{166}Ho-chitosan complex

INTRODUCTION

Stereotactic intracavitary radiation therapy with instillation of radioactive particles can be an

책임저자 : 김은희 서울시 노원구 공릉동 215-4
Tel : 970-1353 Fax : 970-1341
E-mail : ekim@kcchsun.kcch.re.kr

effective method to treat unresectable cystic brain tumor. The first clinical trial of intracavitary irradiation of brain cystic tumor was performed by Lange et al.[1]. They adopted a transphenoidal approach with a small bony opening of the sellar floor, followed by cyst puncture, exclusion of cyst leakage, injection of ^{90}Y-colloid, and finally tight closure of the puncture site. The dosage of ^{90}Y-colloid was determined to deliver 200 Gy of radiation dose to the cyst wall. In the following clinical trial by Liu et al.[2], not only ^{90}Y but also ^{32}P was chosen as the beta-emitting source.

In Korea, intracavitary radiation therapy with Holmium-166 chitosan complex for unresectable cystic brain tumor is considered to be a strong candidate protocol for conventional application. ^{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 9mm of CSDA (continuous slowing down approximation) range in liquid water, (2) half-life of 26.9 hours, and (3) 81-keV g-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,g) ^{166}Ho reaction. The 30MW 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 (NO3) solution at room temperature[3]. 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 tumoral cyst via an Ommaya reservoir installed in subgalea area. After injection, the biodistribution of ^{166}Ho-CHICO can be monitored by gamma camera. Once ^{166}Ho-CHICO is infused into the cyst, beta particles emitted from ^{166}Ho deliver energy both to the cystic fluid and to the cyst wall. The therapeutic response can be evaluated by observing the MRI of the lesion.

In this study, dose to the cyst wall has been estimated by Monte Carlo simulation. A spherical cyst of a varying size (1cm, 2cm, and 3cm in diameter) is the model geometry. The target volume is a spherical shell of 1mm in thickness located at a varying depth from the surface of the cyst wall. Base on this evaluation, one can determine the amount of ^{166}Ho to be administered to lead to the recommended dose of 200 Gy to the cyst wall.

METHODS

When ^{166}Ho-CHICO is infused into the cyst, it is predicted that part of the infused ^{166}Ho-chitosan is bound to the cyst wall surface. Since dose to the cyst wall is attributed to ^{166}Ho both diffused in the cystic fluid and bound to the cyst wall surface, it is important to find the activity density both in the cystic fluid and on the cyst wall surface.

The volume of the cyst can be estimated by measuring the cyst area in each image section obtained by MRI. The values of the cyst perimeter measured in each image section are used to calculate the area of the cyst wall surface. The activity in the cystic fluid is assessed by extracting some cystic fluid, counting the volume activity density, and multiplying it by the

known cyst volume. The fraction of ^{166}Ho-CHICO administered that is bound to the cyst wall surface can be obtained by subtracting the activity in the cystic fluid from the total administered activity. With the known volume of the cyst and the area of the cyst wall surface, the volume activity density of the cystic fluid and the areal activity density of the cyst wall surface can be calculated.

The calculational model is shown in Fig. 1. ^{166}Ho-CHICO is considered to be diffused in the cystic fluid or bound to the cyst wall surface. Dose to the cyst wall is estimated both for ^{166}Ho-CHICO uniformly diffused in the cystic fluid and for ^{166}Ho-CHICO uniformly bound to the cyst wall surface. For a given amount of ^{166}Ho-CHICO injection, the volume activity density of the cystic fluid and the areal activity density of the cyst wall surface are obtained on the basis of the known attachment fraction of ^{166}Ho-CHICO to the cyst wall surface. Dose to the cyst wall is obtained by summing the dose due to ^{166}Ho-CHICO in the cystic fluid and that due to ^{166}Ho-CHICO bound to the cyst wall surface.

Electron transport in soft tissue is simulated using the Monte Carlo code EGS4[4]. The PRESTA version of EGS4 allows tracing electrons until they slow down to 10keV and photons down to 1keV. The range of electrons at 10keV in liquid water is about 2.6mm, which is short enough to describe the local energy deposition in a target volume of cellular level.

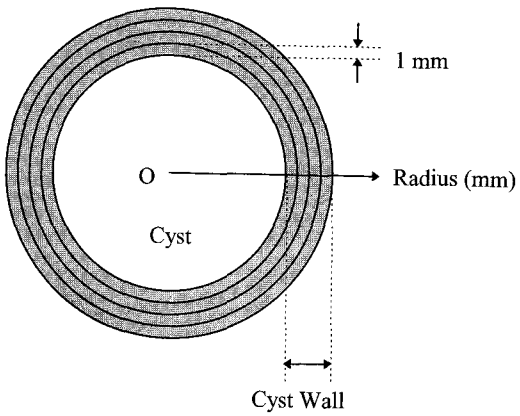

Fig. 1. Geometrical model for calculating dose ω the cyst wall.

RESULTS

Absorbed dose to the cyst wall due to ^{166}Ho-CHICO in the cystic fluid is given in Tables 1 to 3. The ^{166}Ho-CHICO of 10mCi in total activity is assumed to be uniformly distributed in the cyst each of 1cm, 2cm, and 3cm in diameter. As compared to the dose to the innermost target volume within a depth of 1mm, the dose to the target volume at 4mm in depth is reduced to less than 5 percents. When the total energy absorbed in the target volume within 4mm in depth from the cyst wall surface

Table 1. Absorbed Dose to a 1mm-thick Cyst wall at a Varying Depth for a 1cm-dia. Cyst when 10mCi of ^{166}Ho is Uniformly Distributed in the Cystic Fluid

Target depth(mm)	Absorbed dose(Gy)	Relative dose[a]	Cumulative energy absorption[b]
1.0	1283.(2.63%)[c]	100.	58.7
2.0	407.6(1.62%)	31.8	84.8
3.0	132.2(3.38%)	10.3	96.0
4.0	36.7(5.10%)	2.86	100.

[a] : Percent dose relative to dose at 1 mm in depth
[b] : Percent energy absorption relative to total energy absorption within 4 mm in depth
[c] : Percent fractional standard deviation

Table 2. Absorbed Dose to a 1mm-thick Cyst Wall at a Varying Depth for a 2cm-dia. Cyst when 10mCi of ^{166}Ho is Uniformly Distributed in the Cystic Fluid

Target depth(mm)	Absorbed dose(Gy)	Relative dose[a]	Cumulative energy absorption[b]
1.0	141.4(1.92%)[c]	100.	61.2
2.0	48.09(4.64%)	34.0	86.1
3.0	16.64(3.54%)	11.8	96.2
4.0	5.259(5.88%)	3.72	100.

[a] : Percent dose relative to dose at 1mm in depth
[b] : Percent energy absorption relative to total energy absorption within 4mm in depth
[c] : Percent fractional standard deviation

Table 3. Absorbed Dose to a 1mm-thick Cyst Wall at a Varying Depth for a 3cm-dia. Cyst when 10mCi of ^{166}Ho is Uniformly Distributed in the Cystic Fluid

Target depth(mm)	Absorbed dose(Gy)	Relative dose[a]	Cumulative energy absorption[b]
1.0	40.00(4.58%)[c]	100.	60.5
2.0	14.96(4.09%)	37.4	86.2
3.0	5.315(4.72%)	13.3	96.4
4.0	1.660(11.2%)	4.15	100.

[a] : Percent dose relative to dose at 1mm in depth
[b] : Percent energy absorption relative to total energy absorption within 4mm in depth
[c] : Percent fractional standard deviation

Table 4. Absorbed Dose to a 1mm-thick Cyst Wall at a Varying Depth for a 1cm-dia. Cyst when 10mCi of ^{166}Ho is Uniformly Bound to the Cyst wall Surface

Target depth(mm)	Absorbed dose(Gy)	Relative dose[a]	Cumulative energy absorption[b]
1.0	4967.(1.74%)[c]	100.	59.4
2.0	1421.(3.90%)	28.6	83.1
3.0	523.8(2.59%)	10.5	94.7
4.0	184.1(2.19%)	3.71	100.

[a] : Percent dose relative to dose at 1mm in depth
[b] : Percent energy absorption relative to total energy absorption within 4mm in depth
[c] : Percent fractional standard deviation

is normalized to 100%, the energy deposition in each target shell is about 60%, 25%, 10%, and 5% at 1mm, 2mm, 3mm, and 4mm in depth, respectively.

Absorbed dose to the cyst wall due to ^{166}Ho-CHICO bound to the cyst wall surface is given in Tables 4 to 6. The ^{166}Ho-CHICO of 10 mCi in total activity is assumed to be uniformly bound to the cyst wall surface for a cyst each of 1cm-, 2cm-, and 3cm in diameter. As compared to the dose to the innermost target volume within a depth of 1mm, the dose to the target volume at 4mm in depth is reduced to less than 5 percents. When the total energy absorbed in the target volume within 4mm in depth from the cyst wall surface is normalized to 100%, the energy deposition in each target shell is about 60%, 25%, 10%, and 5% at 1mm, 2mm, 3mm, and 4mm in depth, respectively.

Tables 7 and 8 list the values of absorbed dose to the cyst wall at a varying depth for a uniform ^{166}Ho-CHICO source of 1mCi/ml in vo-

Table 5. Absorbed Dose to a 1mm-thick Cyst Wall at a Varying Depth for a 2cm-dia. Cyst when 10mCi of ^{166}Ho is Uniformly Bound to the Cyst Wall Surface

Target depth(mm)	Absorbed dose(Gy)	Relative dose[a]	Cumulative energy absorption[b]
1.0	1317.(.990%)[c]	100.	62.8
2.0	393.0(2.38%)	29.8	85.3
3.0	151.9(4.51%)	11.5	95.5
4.0	56.83(6.67%)	4.31	100.

[a] : Percent dose relative to dose at 1mm in depth
[b] : Percent energy absorption relative to total energy absorption within 4mm in depth
[c] : Percent fractional standard deviation

Table 6. Absorbed Dose to a 1mm-thick Cyst Wall at a Varying Depth for a 3cm-dia. Cyst when 10mCi of ^{166}Ho is Uniformly Bound to the Cyst wall Surface

Target depth(mm)	Absorbed dose(Gy)	Relative dose[a]	Cumulative energy absorption[b]
1.0	601.7(.685%)[c]	100.	63.4
2.0	188.7(2.39%)	31.3	85.9
3.0	73.87(2.17%)	13.0	95.8
4.0	27.80(3.25%)	4.62	100.

[a] : Percent dose relative to dose at 1mm in depth
[b] : Percent energy absorption relative to total energy absorption within 4mm in depth
[c] : Percent fractional standard deviation

Table 7. Absorbed Dose(Gy) to a 1mm-thick Cyst Wall at a Varying Depth for 1mCi/ml of ^{166}Ho Uniformly Distributed in the Cystic Fluid

Target depth(mm)	1cm-dia. cyst	2cm-dia. cyst	3cm-dia. cyst
1.0	67.18(2.63%)[a]	59.24(1.92%)	56.64(4.58%)
2.0	21.34(1.62%)	20.14(4.64%)	21.15(4.09%)
3.0	6.923(3.38%)	6.968(3.54%)	7.513(4.72%)
4.0	1.920(5.10%)	2.202(5.88%)	2.347(11.2%)

[a] : Percent fractional standard deviation

lume activity density and for a uniform ^{166}Ho-CHICO source of 0.1mCi/cm^2 in areal activity density, respectively. Among cysts of different sizes, the same volume activity density and the same areal activity density result in similar dose values to the cyst wall.

About 98.1% of attachment fraction of ^{166}Ho-CHICO to the cyst wall surface was observed from one clinical case. Also, the CT image of the lesion has shown that ^{166}Ho-CHICO is confined within the cyst without leakage. Consider that 10mCi of ^{166}Ho-CHICO is injected into a cyst of 3cm in diameter. Assuming 98.1% attachment fraction and uniform ^{166}Ho-CHICO distribution both in the cystic fluid and on the cyst wall surface, the initial volume and the initial areal activity density are 0.0134mCi/cm^3 and 0.347mCi/cm^2, respectively. In this case, the volume source leads to 0.759Gy, 0.283Gy, 0.101Gy, and 0.0314Gy of absorbed dose to the cyst wall at every 1mm in depth, respectively. The surface source leads to 590Gy, 185Gy, 72.5Gy, and 27.3Gy of absorbed dose to the cyst wall at every 1mm in depth, respectively. The

Table 8. Absorbed Dose(Gy) to a 1mm-thick Cyst Wall at a Varying Depth for 0.1mCi/cm^2 of ^{166}Ho Uniformly Bound to the Cyst Wall Surface

Target depth(mm)	1cm-dia. cyst	2cm-dia. cyst	3cm-dia. cyst
1.0	156.1(1.74%)[a]	165.5(.990%)	170.1(.685%)
2.0	44.63(3.90%)	49.39(2.38%)	53.33(2.39%)
3.0	16.45(2.59%)	19.09(4.51%)	20.89(2.17%)
4.0	5.785(2.19%)	7.139(6.67%)	7.860(3.25%)

[a] : Percent fractional standard deviation

total absorbed dose to the cyst wall is, therefore, 591.8Gy, 185.3Gy, 72.60Gy, and 27.33Gy at 1mm, 2mm, 3mm, and 4mm in depth, respectively.

If the attachment of ^{166}Ho-CHICO to the cyst wall surface is not recognized, the whole ^{166}Ho-CHICO administered would be considered as a volume source diffused in the cystic fluid. With 10mCi of ^{166}Ho-CHICO uniformly diffused in the cyst of 3cm in diameter, the volume activity density of the cystic fluid is 0.707mCi/cm^3. Absorbed dose to the cyst wall is estimated 40.06Gy, 14.96Gy, 7.513Gy, and 1.660Gy at every 1mm in depth from the cyst wall surface, respectively. The absorbed dose to the cyst wall would be underestimated by 90% to 94% by ignoring the attachment of ^{166}Ho-CHICO to the cyst wall surface.

DISCUSSION

This paper deals with a spherical model of cystic brain tumor. In real clinical applications, the tumoral cyst is less likely spherical. Nonetheless, the spherical geometry is a reasonable choice to represent the cyst of a random geometry. Studies with other geometry models of cyst would add to the dose estimate library, which allows utilizing data for a geometry most close to the real one in determining the activity to be administered.

The comparison of dose estimates among cysts of different sizes (1cm, 2cm and 3cm in diameter) for a standard volume or areal activity density helps understanding the relationship between the activity administered and the resulting dose to the cyst wall. Data in Table 7 imply that the volume activity density can be a major parameter determining the dose to the cyst wall contributed by the radioactive source diffused in the cystic fluid regardless of the total activity and the cyst size. In the same coin, data in Table 8 show that the areal activity density over the cyst wall surface can suggest the energy density in the cyst wall delivered from the surface source regardless of the total activity and the cyst size. This fact indicates that the dose to the cyst wall for a cyst of an arbitrary size can be approximated by converting the total activity either diffused in the cystic fluid or bound to the cyst wall surface into a volume activity density or an areal activity density, respectively, and comparing those with the standard activity density values assumed in Tables 7 and 8.

SUMMARY

^{166}Ho-chitosan complex, or ^{166}Ho-CHICO, is a candidate pharmaceutical for intracavitary radiation therapy of cystic brain tumors because of the desirable nuclear characteristics of ^{166}Ho for therapeutic use and the suitable biological and chemical characteristics of chitosan, not to

mention its ready producibility. The amount of ^{166}Ho-CHICO to be administered to obtain the goal therapeutic effect can be suggested by predicting the dose to the cyst wall for a varying pharmaceutical dose. When ^{166}Ho-CHICO is infused into the cyst, the major part of the energy delivery by beta particles emitted from ^{166}Ho occurs in the cyst wall within 4mm in depth from the cyst wall surface. Also, realizing the attachment of ^{166}Ho-CHICO to the cyst wall surface would change the predictions of dose to the cyst wall.

REFERENCES

1) Lange M, Kirsch CM, Steude U, Oeckler R : *Intracavitary treatment of intrasellar cystic craniopharyngeomas with 90-Yttrium by trans sphenoidal approacha technical note. Acta Neutochir Wien 1995;135(3-4):206-209*
2) Liu Z, Tian Z, Yu X, Li S, Huang H, Kang G, Xu Y, Wang Y : *Stereotactic intratumour irradiation with nuclide for craniopharyngiomas. Chin Med J Engl 1996;109(3):219-222*
3) 박경배, 김영미, 신병철, 김재록 : 새로운 내부 방사선 치료용 *166Ho-Chitosan* 착물 및 그 응집입자의 제조에 관한 연구. 대한핵의학회지 *1996;30(3):351-360*
4) Nelson WR, Hyrayama H, Rogers DWO : *The EGS4 code system. Stanford Linear Accelerator Center 1985;SLAC-265*