**Table 3** Univariate and multivariate analysis of potential predictive factors influencing LCR*

| | LCR | | | | | |
|---|---|---|---|---|---|---|
| Factors | 2-y | *P* value in uni | *P* value in multi | Hazard ratio | 95% CI | |
| Gender | | | | | | |
| Male | 36.2 | .462 | | | | |
| Female | 29.4 | | | | | |
| Laterality | | | | | | |
| Bilateral | 38.9 | .017* | .133 | | | |
| Unilateral | 15.0 | | | | | |
| ICRB at initial presentation | | | | | | |
| Group A/B | 53.3 | .022* | .001* | 10.323 | 2.737 | 38.932 |
| Group C/D/E | 24.1 | | | | | |
| ICRB at brachytherapy | | | | | | |
| Group A/B | 55.9 | <.001* | .027* | 0.441 | 0.213 | 0.911 |
| Group C/D/E | 20.7 | | | | | |
| Applicator type | | | | | | |
| CIA/CCA | 42.1 | .141 | | | | |
| CIB/CCB | 26.0 | | | | | |
| Prior EBRT | | | | | | |
| Yes | 32.0 | .707 | | | | |
| No | 35.7 | | | | | |
| Treatment type | | | | | | |
| First-line/second-line | 27.1 | .152 | | | | |
| Salvage | 45.5 | | | | | |
| Vitreous seeding at brachytherapy | | | | | | |
| Yes | 18.9 | .016* | .892 | | | |
| No | 43.6 | | | | | |
| Subretinal seeding at brachytherapy | | | | | | |
| Yes | 19.2 | .04* | .785 | | | |
| No | 39.4 | | | | | |
| Response to preceding therapy | | | | | | |
| Good | 43.8 | .116 | | | | |
| Stable/poor | 28.6 | | | | | |
| Tumor size at brachytherapy (DD) | | | | | | |
| <5 DD | 52.5 | .001* | .252 | | | |
| ≧5 DD | 19.6 | | | | | |
| Dose rate at outer surface of sclera | | | | | | |
| <3 Gy/h | 29.5 | .271 | | | | |
| ≧3 Gy/h | 36.4 | | | | | |
| Reference depth | | | | | | |
| <5 mm | 47.1 | .01* | .295 | | | |
| ≧5 mm | 21.4 | | | | | |
| Dose rate at reference depth | | | | | | |
| <0.7 Gy/h | 17.9 | .011* | .105 | | | |
| ≧0.7 Gy/h | 40.4 | | | | | |
| Dose at reference depth (Gy) | | | | | | |
| <35 Gy | 11.8 | .008* | .448 | | | |
| ≧35 Gy | 37.9 | | | | | |
| Dose at reference depth ($BED_{10}$) | | | | | | |
| <40 $Gy_{10}$ | 0.0 | .001* | .034* | 2.237 | 1.063 | 4.710 |
| ≧40 $Gy_{10}$ | 36.9 | | | | | |
| Treatment time | | | | | | |
| <53 h | 37.8 | .195 | | | | |
| ≧53 h | 29.8 | | | | | |

*Abbreviations:* BED = biological effective dose; CCA = ■; CI = confidence interval; CIA = ■; CIB = ■; CBB = ■; DD = disc diameter; EBRT = external beam radiation therapy; ICRB = the International Classification of Retinoblastoma; LCR = local control rate; multi = multivariate analysis; uni = univariate analysis.

* $P<.05$.

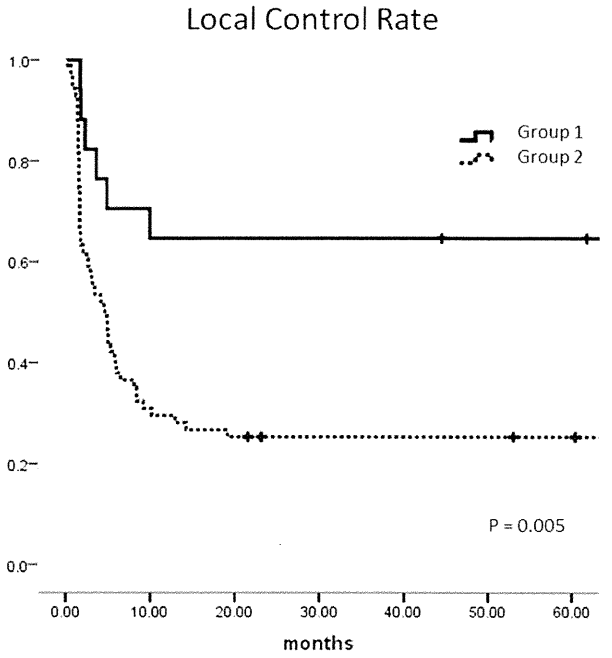



**Fig. 2.** Local control rate (LCR) according to the group classification by the International Classification of Retinoblastoma and biological effective dose (BED) with $\alpha/\beta = 10$ Gy of the reference depth (for details refer to the text).

control. Both reference depth and dose rate at reference depth were prognostic factors of local control suggesting that physical limitation of RPT, which is not suitable for treating tall tumors as previously reported (8-11).

The administration of previous EBRT did not influence LCR (Table 3), suggesting that response to RPT did not differ between relapsed or refractory tumors after EBRT and radiation-naive tumors as previously reported (9).

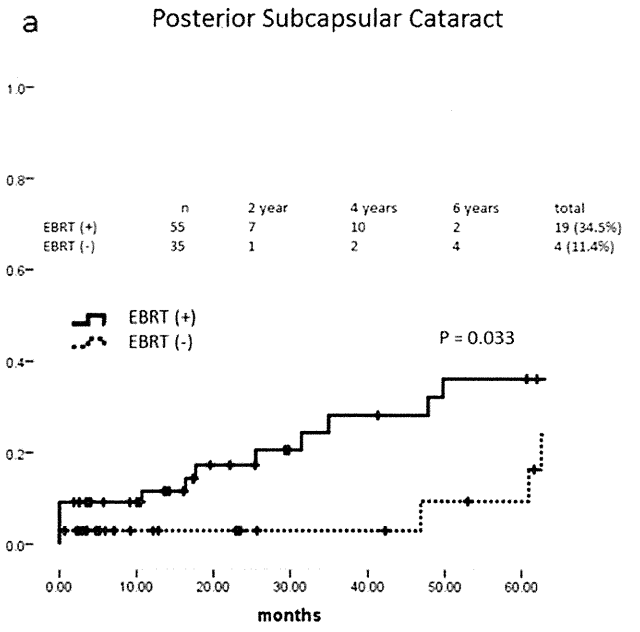
Concerning the morbidities, the incidence of posterior subcapsular cataract was influenced by EBRT but not by RPT whose dose to the lens is negligible. In the current study, the incidence of proliferative retinopathy was as low as 6.7%, which is similar to the low reported incidence of 2.4% in Abouzeid's study. In contrast, the incidence was reported to be as high as 17.1% in the series by Schueler et al in which a higher dose was employed. Proliferative retinopathy has been reported to occur in 13%-19% after $^{125}$I plaque brachytherapy in which dose reached further than $^{106}$Ru.

$BED_3 \geqq 1200$ $Gy_3$ of the outer surface of sclera was significantly correlated with the incidence of either retinal detachment or proliferative retinopathy or rubeosis (Fig. 3b). A higher dose for sclera was demonstrated to cause late complications associated with RPT; therefore, it is important to exclude tall tumors whose dose of the outer surface of sclera will be high in order to avoid complications. However, there were only 2 enucleations caused by the late complications of RPT, and RPTs were generally well tolerated.

There were 2 secondary malignancies in the current series. Both of them occurred in the patients with a hereditary retinoblastoma, 1 of them developed within the EBRT fields. In accordance with the literature (6, 7), plaque brachytherapy itself did not seem to increase the incidence of secondary malignancy.

## Conclusion

RPT is an effective and safe focal therapy for retinoblastoma. However, optimal dose of RPT remains to be studied further.



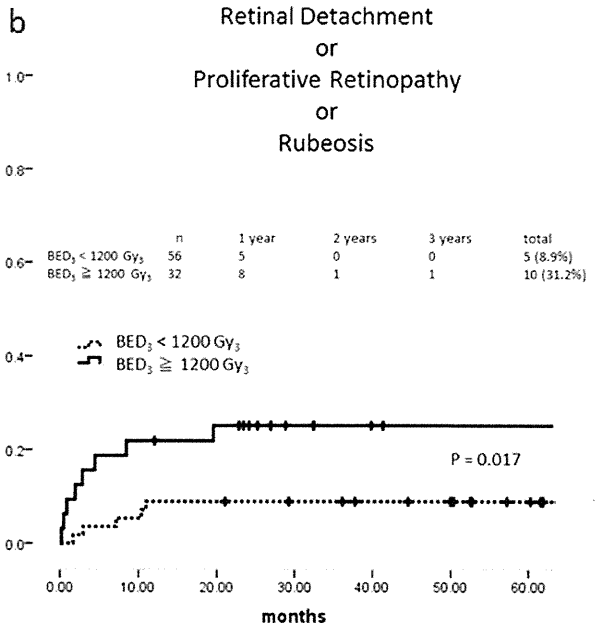




**Fig. 3.** (a) Cumulative incidence of posterior subcapsular cataract according to whether external beam radiation therapy (EBRT) was administered. (b) Cumulative incidence of retinal detachment, proliferative retinopathy and rubeosis stratified by biological effective dose (BED) with $\alpha/\beta = 3$ Gy at the outer surface of sclera.

## References


1. National registry of retinoblastoma in Japan (1975–1982). The Committee for the National Registry of Retinoblastoma. *Nippon Ganka Gakkai Zasshi* 1992;96:1433-1442.
2. Kleinerman RA, Tucker MA, Tarone RE, et al. Risk of new cancers after radiotherapy in long-term survivors of retinoblastoma: an extended follow-up. *J Clin Oncol* 2005;23:2272-2279.
3. Abramson DH, Schefler AC. Update on retinoblastoma. *Retina* 2004; 24:828-848.
4. Lin P, O'Brien JM. Frontiers in the management of retinoblastoma. *Am J Ophthalmol* 2009;148:192-198.
5. Freire JE, De Potter P, Brady LW, et al. Brachytherapy in primary ocular tumors. *Semin Surg Oncol* 1997;13:167-176.
6. Shields CL, Shields JA, Cater J, et al. Plaque radiotherapy for retinoblastoma: long-term tumor control and treatment complications in 208 tumors. *Ophthalmology* 2001;108:2116-2121.
7. Shields CL, Mashayekhi A, Sun H, et al. Iodine 125 plaque radiotherapy as salvage treatment for retinoblastoma recurrence after chemoreduction in 84 tumors. *Ophthalmology* 2006;113:2087-2092.
8. Schueler AO, Fluhs D, Anastassiou G, et al. Beta-ray brachytherapy with 106Ru plaques for retinoblastoma. *Int J Radiat Oncol Biol Phys* 2006;65:1212-1221.
9. Abouzeid H, Moeckli R, Gaillard MC, et al. (106)Ruthenium brachytherapy for retinoblastoma. *Int J Radiat Oncol Biol Phys* 2008;71: 821-828.
10. Nag S, Quivey JM, Earle JD, et al. The American Brachytherapy Society recommendations for brachytherapy of uveal melanomas. *Int J Radiat Oncol Biol Phys* 2003;56:544-555.
11. Jarvien H, Cross WG, Soares C, et al. Dosimetry of beta rays and low-energy photons for brachytherapy with sealed sources. *J ICRU* 2004;4: 2-175.
12. Linn Murphree A. Intraocular retinoblastoma: the case for a new group classification. *Ophthalmol Clin North Am* 2005;18:41-53. viii.
13. Shields CL, Mashayekhi A, Au AK, et al. The International Classification of Retinoblastoma predicts chemoreduction success. *Ophthalmology* 2006;113:2276-2280.
14. BEBIG. BEBIG Ruthenium Augenapplikatoren Kundeninformation: Einführung der neuen NIST-kalibrierten Dosimetrie Einführung der neuen PTB-kalibrierten Aktivitätsmessungen. 2002:version 1.03 v. 12.11.02.
15. Dale RG. The application of the linear-quadratic dose-effect equation to fractionated and protracted radiotherapy. *Br J Radiol* 1985;58:515-528.
16. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457-481.
17. Yamane T, Kaneko A, Mohri M. The technique of ophthalmic arterial infusion therapy for patients with intraocular retinoblastoma. *Int J Clin Oncol* 2004;9:69-73.
18. Oosterhuis JA, Journee-de Korver HG, Kakebeeke-Kemme HM, et al. Transpupillary thermotherapy in choroidal melanomas. *Arch Ophthalmol* 1995;113:315-321.
19. Foote RL, Garretson BR, Schomberg PJ, et al. External beam irradiation for retinoblastoma: patterns of failure and dose-response analysis. *Int J Radiat Oncol Biol Phys* 1989;16:823-830.
20. Hernandez JC, Brady LW, Shields JA, et al. External beam radiation for retinoblastoma: results, patterns of failure, and a proposal for treatment guidelines. *Int J Radiat Oncol Biol Phys* 1996;35: 125-132.

JJCO Japanese Journal of Clinical Oncology

*Jpn J Clin Oncol 2011;41(9)1119–1126*
*doi:10.1093/jjco/hyr096*

# A Consensus-based Guideline Defining Clinical Target Volume for Primary Disease in External Beam Radiotherapy for Intact Uterine Cervical Cancer

**Takafumi Toita[1,*], Tatsuya Ohno[2], Yuko Kaneyasu[3], Tomoyasu Kato[4], Takashi Uno[5], Kazuo Hatano[6], Yoshiki Norihisa[7], Takahiro Kasamatsu[4], Takeshi Kodaira[8], Ryoichi Yoshimura[9,10], Satoshi Ishikura[11] and Masahiro Hiraoka[7] for the JCOG Radiation Therapy Study Group**

[1]Department of Radiology, Graduate School of Medical Science, University of the Ryukyus, Okinawa, [2]Gunma University Heavy Ion Medical Center, Gunma University, Maebashi, [3]Department of Radiation Oncology, Graduate School of Biomedical Sciences, Hiroshima University, Hiroshima, [4]Division of Gynecology, National Cancer Center Hospital, Tokyo, [5]Department of Radiology, Graduate School of Medicine, Chiba University, [6]Division of Radiation Oncology, Chiba Cancer Center, Chiba, [7]Department of Radiation Oncology and Image-applied Therapy, Kyoto University Graduate School of Medicine, Kyoto, [8]Department of Radiation Oncology, Aichi Cancer Center, Nagoya, [9]Department of Radiology, Tokyo Medical and Dental University, [10]Department of Radiation Oncology, National Cancer Center Hospital, Tokyo, and [11]Department of Radiology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan

*For reprints and all correspondence: Takafumi Toita, Department of Radiology, Graduate School of Medical Science, University of the Ryukyus, 207 Uehara, Nishihara-cho, Okinawa 903-0215, Japan.
E-mail: b983255@med.u-ryukyu.ac.jp

Received April 25, 2011; accepted June 9, 2011

**Objective:** To develop a consensus-based guideline to define clinical target volume for primary disease (clinical target volume primary) in external beam radiotherapy for intact uterine cervical cancer.
**Methods:** The working subgroup of the JCOG Radiation Therapy Study Group began developing a guideline for primary clinical target volume in November 2009. The group consisted of 10 radiation oncologists and 2 gynecologic oncologists. The process started with comparing the contouring on computed tomographic images of actual cervical cancer cases among the members. This was followed by a comprehensive literature review that included primary research articles and textbooks as well as information on surgical procedures. Extensive discussion occurred in face-to-face meetings (three occasions) and frequent e-mail communications until a consensus was reached.
**Results:** The working subgroup reached a consensus on the definition for the clinical target volume primary. The clinical target volume primary consists of the gross tumor volume, uterine cervix, uterine corpus, parametrium, vagina and ovaries. Definitions for these component structures were determined. Anatomical boundaries in all directions were defined for the parametrium. Examples delineating these boundaries were prepared for the posterior border of the parametrium for various clinical situations (i.e. central tumor bulk, degree of parametrial involvement).
**Conclusions:** A consensus-based guideline defining the clinical target volume primary was developed for external beam radiotherapy for intact uterine cervical cancer. This guideline will serve as a template for radiotherapy protocols in future clinical trials. It may also be used in actual clinical practice in the setting of highly precise external beam radiotherapy, including intensity-modulated radiotherapy.

*Key words: cervical cancer – radiation therapy – clinical target volume – contouring*

## INTRODUCTION

Standard radiotherapy for cervical cancer patients consists of external beam whole pelvic radiotherapy (EBRT) and intracavitary brachytherapy (1). Recently, treatment planning for both modalities has been shifting away from conventional two-dimensional planning to volume-based three-dimensional (3D) planning (2,3). Three-dimensional planning should achieve appropriate target coverage within sufficient doses and effective sparing of organs at risk (OARs). Intensity-modulated radiation therapy (IMRT) is the most promising 3D EBRT method, and its use has been increasing in actual clinical practice in the USA (4) and other countries. Several investigators reported promising treatment results in terms of reduced toxicity for patients with uterine cervical cancer (5–7). In Japan, IMRT has been covered by the public insurance system since April 2010 for all cancer patients. Therefore, as is now the case for other solid malignancies, the use of IMRT should be promoted for cervical cancer patients. To correctly deliver IMRT, an accurate and reproducible contouring of the clinical target volume (CTV) is primarily important and essential. There is, however, a degree of uncertainty in the delineation of the CTV (8). To achieve consistent CTV delineations, which minimize unexpected variation, consensus guidelines have been published for the pelvic lymph node CTV (9–11). A working subgroup for developing a consensus-based guideline on the CTV for cervical cancer was organized within the Radiation Therapy Study Group (RTSG) of the Japan Clinical Oncology Group (JCOG) in July 2008. The subgroup has already published a guideline on pelvic node CTV (12). More recently, the Radiation Therapy Oncology Group (RTOG) in the USA published guidelines regarding primary tumor CTV (CTV primary) for intact uterine cervical cancer (13). We have also conducted a study to establish a CTV primary guideline to perform appropriate contouring of the CTV primary in actual clinical practice as well as in the setting of clinical trials with IMRT. This paper describes the process used to develop the guideline, as well as examples of CTV delineation schemes.

## PATIENTS AND METHODS

The working subgroup, which was formed to establish a consensus-based guideline on the CTV for EBRT in cervical cancer, started working on the CTV for primary lesions (CTV primary) in November 2009. In addition to the original seven members, five members consisting of three radiation oncologists and two gynecologic oncologists joined the committee. The members had three face-to-face meetings and extensive discussions via e-mail throughout the working process.

In the first meeting, a brainstorming discussion was held with review of the CTV definitions of image-guided intracavitary brachytherapy (IGBT) for cervical cancer (14–16), and the CTV primaries of other disease sites, e.g. head and neck, and prostate (17). After this meeting, electronic copies of computed tomographic (CT) and magnetic resonance imaging (MRI) images of two actual patients were distributed to the members. Each member then independently made his or her own CTV primary delineations on the CT images. The contoured images were then reviewed in the second meeting. Some areas of discrepancy were observed in the CTV primary delineations (Fig. 1a and b). Following extensive discussion to reach consensus, drafts of the definitions of structures composing the CTV primary and actual figures were prepared by a principal investigator (T.T.) referring to the RTOG guidelines (13). These were presented and reviewed at the JCOG RTSG meeting in November 2010. These were then refined further through additional e-mail discussions. A consensus among the working group members was nearly reached in the third meeting. Any remaining discrepancies were addressed through subsequent e-mail discussions. A final version of the consensus-based guideline on the CTV primary was established in February 2011.

## RESULTS

### Components for the CTV Primary

The CTV primary consists of the gross tumor volume of the primary tumor (GTV primary), uterine cervix, uterine corpus, parametrium, vagina and ovaries.

### Definitions for Each Component Structure of the CTV Primary

#### *GTV Primary*

The GTV primary includes gross disease visible on an MRI T2-weighted image (T2WI) and lesions detected by clinical examinations.

#### *Uterine Cervix*

The entire cervix, if not already included within the GTV contour, is to be contoured (13). The cranial margin is defined at the level at which the uterine arteries enter the uterus (same level of the superior border of the parametrium CTV).

#### *Uterine Corpus*

No CTV margin should be added to the visualized corpus on CT images, even for cases in which the tumor has significant corpus invasion. This decision was based on the fact that the majority of the uterine corpus is suspended within the pelvic cavity without surrounding the connective tissue.

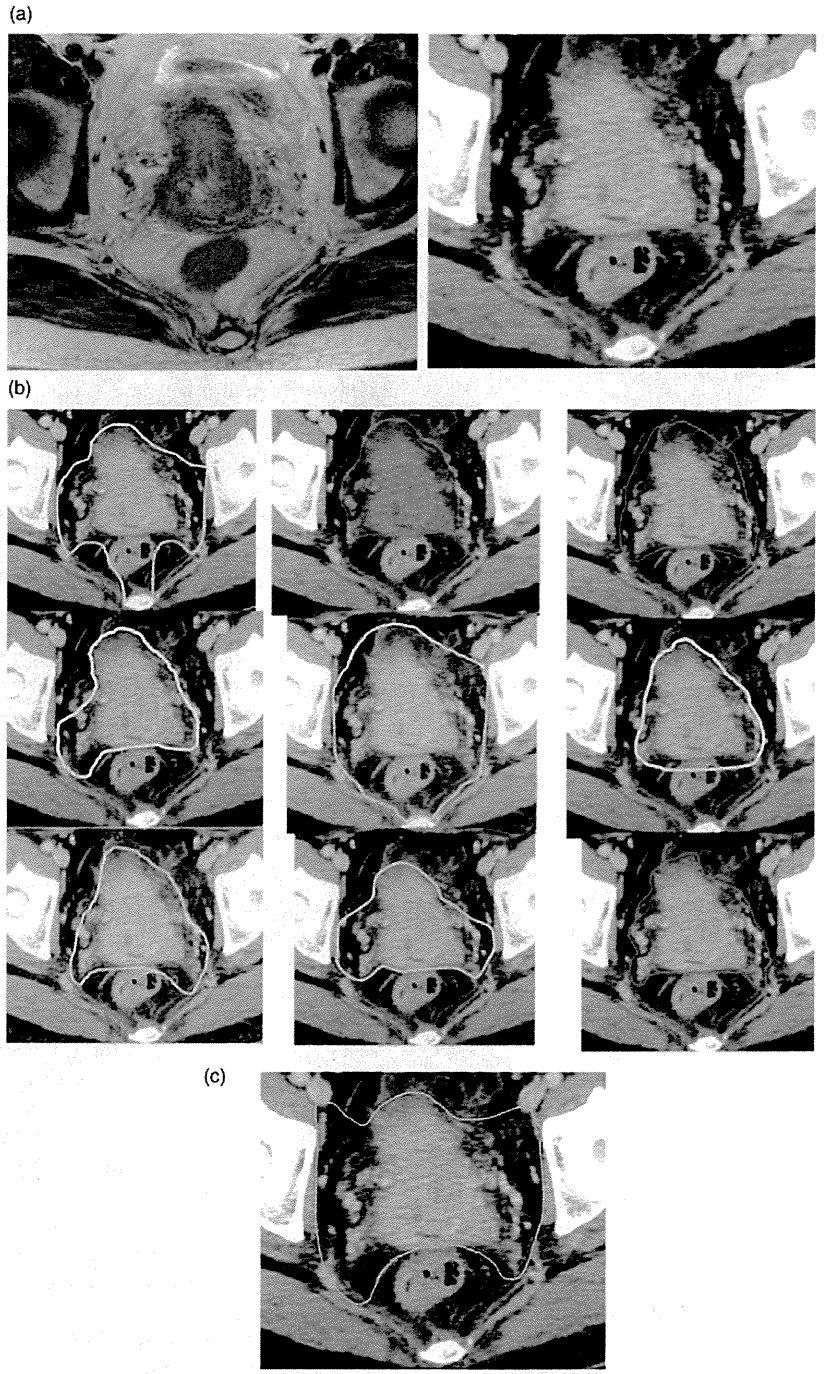



**Figure 1.** (a) Magnetic resonance imaging (MRI) and computed tomographic (CT) slices of a FIGO Stage IIIB cervical cancer patient who demonstrated bilateral parametrial invasion with nodular fixation to the right pelvic wall on pelvic exam. Clinical information for this patient was also distributed to the nine working group members along with the CT and MRI images. (b) CT images with the primary clinical target volume (CTV) contouring drawn by the working group members, which reveal substantial contouring variations among the members. (c) The same CT image with the primary CTV contouring following the present guideline.

**Table 1.** Anatomical boundaries of clinical target volume for parametrium

| Margin | Structures |
|---|---|
| Cranial | Isthmus of uterus (=level where uterine artery drains into) |
| | *Contouring would stop at the level where bowel loops are seen |
| Caudal | Medial boarder of levator ani (Fig. 5) |
| Anterior | Posterior boarder of bladder or posterior boarder of external iliac vessels |
| Posterior | Anterior part (semicircular) of mesorectal fascia |
| | *In case with bulky central tumor or significant parametrial invasion, some modification would be considered (Figs 3 and 4) |
| Lateral | Medial edge of internal obturator muscle, piriformis muscle, coccygeus muscle and ischial ramus |

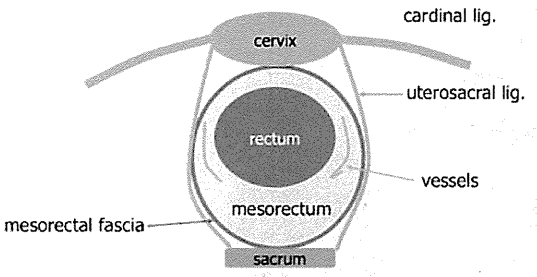



**Figure 2.** An illustration of the anatomical components around the cervix with reference to the parametrium.

The broad ligaments, round ligaments and ovarian ligaments do not need to be included.

Consensus was not reached regarding feasibility of excluding some portions of the uterine corpus (e.g. fundus) from the CTV primary in selected cases (i.e. non-bulky Stage I or II cases who may be candidates for radical trachelectomy).

*Parametrium*

Adipose tissues between the cervix and pelvic wall are included as well as visible linear structures that run laterally (e.g. vessels, nerves and fibrous structures).

Overlapping between the nodal CTV and the parametrium CTV is feasible (13).

Boundary structures of the parametrium CTV for each direction are listed in Table 1. Figure 2 shows a scheme of anatomical components around the cervix with reference to the parametrium. Figures 3a and 4a show a scheme and actual delineation for the posterior border of the parametrium, respectively. Some variations are prepared as determined by the central tumor bulk or parametrial involvement status for the posterior boundary of the parametrium CTV (Figs 3 and 4). The CTV margin could be increased in the posterior direction into the perirectum (Figs 3b and 4b) and/or along the uterosacral ligaments (Figs 3c and d, and 4c and d). Figure 5 shows the primary CTV contouring at the level of the levator ani.

*Vagina*

Paravaginal tissue would be included as well as the vaginal wall. The caudal level should be individually determined based on the findings of both the MRI and clinical examinations. Arrangements of the caudal level according to the status of vaginal invasion are stated as per the RTOG guidelines (13):

Minimal or no vaginal extension: upper half of the vagina
Upper vaginal involvement: upper two-thirds of the vagina
Extensive vaginal involvement: entire vagina

*Ovary*

Ovaries visible on the CT/MRI would be included.

A consensus was not reached regarding the possibility of excluding the ovaries in selected cases (i.e. non-bulky Stage I or II cases with squamous cell carcinoma).

An Example of the CTV Primary Delineation (Fig. 1c)

Figure 1c shows an example of the CTV primary delineation in accordance with the definition developed (on the same slice used in the previous comparison test).

## DISCUSSION

The working subgroup developed a consensus-based guideline for the delineation of the CTV primary for EBRT in patients with intact uterine cervical cancer. The guideline describes the anatomical components to be included in the CTV primary, as well as the definitions for each component. Examples of CTV delineation are also included.

The guideline states that the CTV primary consists of the GTV primary, uterine cervix, uterine corpus, parametrium, vagina and ovaries. This concept seems to be almost the same with surgical treatment: radical hysterectomy, which is a standard surgical procedure for invasive cervical cancer, also includes resection of these structures.

Anatomically, the uterine corpus is concealed within the broad ligament and suspended in the pelvis. This means that no surrounding connective tissues are visible around the corpus on CT or MRI. Therefore, the guideline states that no margin should be added to the visualized corpus for the CTV. We also reached a consensus that the fallopian tubes and round ligaments would not be included in the CTV, in agreement with the RTOG guidelines (13).

The most challenging issue was delineating the parametrium and defining its anatomical boundaries on CT. This difficulty was caused by the limited information of diagnostic radiology to illustrate the relationship between transverse images and the actual parametrial anatomy. In our preliminary comparison of each member's CTV contouring,

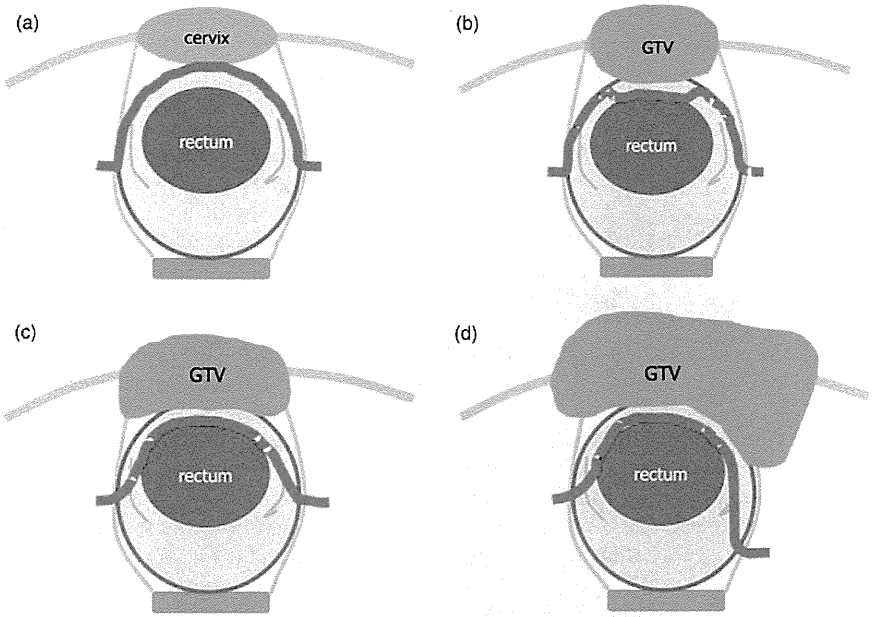



**Figure 3.** Stage-specific delineation schemes for the posterior border of the parametrium (solid red line). (a) Non-bulky early-stage (IB1 or IIA1) disease. (b) Bulky early-stage (IB2 or IIA2) disease. (c) Stage IIB disease (slight parametrial involvement). (d) Stage IIIB disease (massive parametrial involvement).

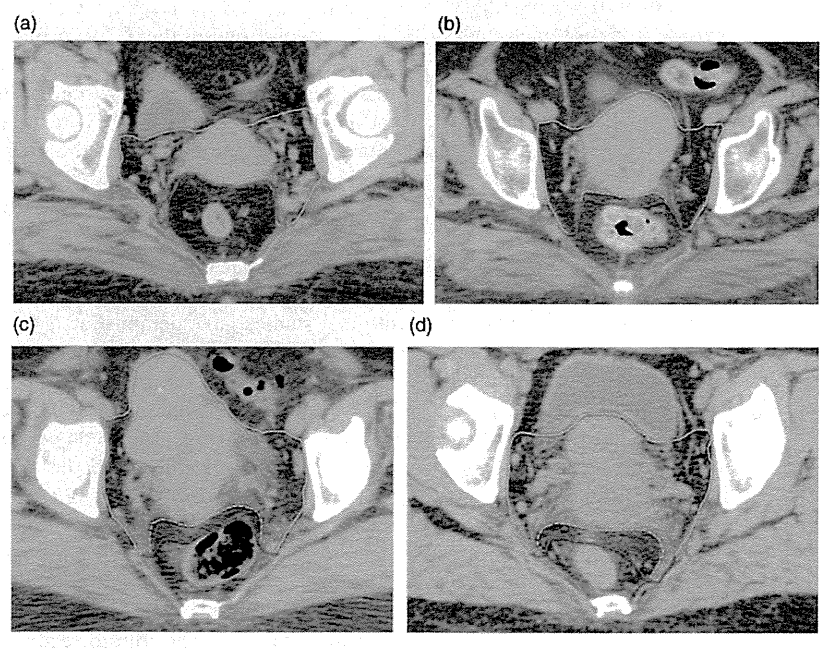



**Figure 4.** Actual delineations of the primary CTV (solid orange line) and posterior border of the parametrium (solid red line) according to disease status Dotted orange lines indicate the anterior border of the perirectum. (a) A case with non-bulky Stage IB1 disease. (b) A case with bulky Stage IB2 disease. (c) A case with Stage IIB disease (bilateral parametrial involvement on pelvic exam). (d) A case with Stage IIIB disease (massive parametrial involvement with fixation to the left pelvic wall on pelvic exam).

significant variations were observed for the parametrium. Lim et al. (13) reported a similar wide range of variation among the WG members in the RTOG. The present discrepancies were resolved through reviewing the anatomical (18–20) and surgical (21) literatures. In the present work, two gynecologic oncologists participated in addition

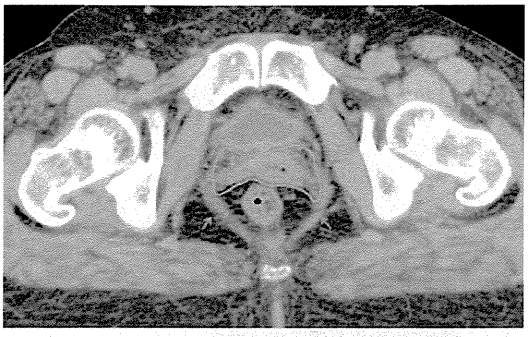


**Figure 5.** An actual delineation of the primary CTV (solid orange line) at the level of the levator ani (blue arrows).

to the radiation oncologists. They contributed valuable information regarding surgical findings, which was instrumental for developing anatomically appropriate definitions of the boundaries. We believe that the participation of surgical oncologists is essential for the design of clinically reliable CTV definitions and contouring atlases.

The anterior and lateral boundaries are virtually identical to those specified by the RTOG guidelines (13). Minor adjustments were made to the lateral definition in the present guideline. The medial edges of the piriformis and coccygeus muscles were added to the lateral boundary. The RTOG guidelines state that the caudal margin of the parametrium is the urogenital diaphragm (13). However, the term 'urogenital diaphragm' usually indicates the inferior surface of the pelvic diaphragm. Therefore, we consider the superior surface of the pelvic diaphragm, which corresponds to the medial edge of the levator ani, a more appropriate term for the definition.

To determine the cranial boundary of the parametrium, we also reviewed the anatomy of the uterus and surrounding structures including the parametrium. The broad ligaments are formed by the peritoneum covering the uterine body and the parametrium (18,20). Instead of using the top of the fallopian tube/broad ligament for the cranial parametrial margin, as specified in the RTOG guidelines (13), we elected to use the cranial margin of the cervix. In an anatomical view, this margin corresponds to the isthmus of the uterus (18); however, the margin is not recognized on CT images. Therefore, the junction of the uterine artery with the uterus was proposed to be the cranial margin of the cervix. This parameter must be evaluated further clinically to ascertain the degree of variability associated with this definition.

There was extensive discussion concerning the posterior boundary of the parametrium. The RTOG guidelines use the uterosacral ligament as one of the boundaries (13). The uterosacral ligaments, however, are not always identifiable on CT images. In contrast, the mesorectal fascia is visible on the CT images in most cases. Chen et al. (22) have demonstrated that 95 and 97.5% of the CT and MRI studies, respectively, show the fascia encircling the rectum and perirectal adipose tissue as either a continuous or interrupted line. They have also shown in a cadaveric space perfusion study that the perirectal space is completely separated from the pararectal space (outside the mesorectum) by the mesorectal fascia (22). Therefore, we selected the semicircular, anterior portion of the mesorectal fascia as the posterior boundary. The RTOG guidelines include an optional definition for Stage IIIB cases (13). We also include additional areas in the parametrium CTV in cases with a bulky cervical tumor or extensive parametrial involvement. Furthermore, we developed protocol variations to address specific situations. Chao et al. (23) stressed the importance of delivering an adequate dose to the uterosacral space for patients with uterosacral space involvement. In contrast, the RTOG guidelines recommend that the entire mesorectal space be included for patients with Stage IIIB or higher disease. We consider this to be excessive. Kato et al. (24) reported clinical outcomes for locally advanced cervical cancer patients (Stage IIB–IVA) treated with carbon ion radiotherapy. Although the posterior part of the mesorectum was not included within the CTVs, favorable local control was reported in their series (24). These results appear to support our opinion. Careful evaluation is warranted to determine whether the entire mesorectal space should be included in the CTV for patients with massive parametrial involvement, and additional discussion is still required to achieve a consensus.

Another challenge in the development of the guideline is the subdefinition of the CTV primary according to the disease status of each patient. Three-dimensional EBRT, notably IMRT, has the ability to precisely exclude structures not intended to be irradiated. There are at least two potential areas for individualization of the CTV primary in uterine cervical cancer. The first is to permit the exclusion of the ovaries. If the ovaries were excluded from the CTV primary, the planning target volume (PTV) would be smaller. The small PTV may result in lower doses and volumes delivered to the surrounding OARs. This option is feasible as several surgical studies have demonstrated that patients with early-stage cervical squamous cell cancer rarely have ovarian metastases (25,26). The second issue pertains to whether a portion of the uterine corpus may be excluded from the CTV primary. Uterine corpus exclusion may also achieve a significant decrease in the doses to the surrounding OARs. As mentioned in the previous RTOG guidelines (13), excluding a portion of the corpus would be an option for selected cases when sufficient data are available regarding the incidence and exact location of uterine recurrence after conservative surgical procedures (e.g. radical trachelectomy) (27). Although we were not able to reach a consensus on these issues, the discussion continues. For these situations, subdivision of the CTV based on risk estimation of disease (i.e. high-, intermediate- and low-risk CTV) may be considered. The CTV primary definitions on IGBT may serve as a reference for this concept (14,15).

Although the CTV delineation for 3D EBRT planning is performed primarily based on CT/MRI findings, some small or superficial lesions may only be detected by a clinical

examination. These small/superficial lesions should also be included in the GTV. This has been addressed in the present guideline. Generally, the CTV delineation is performed on CT images. It is, however, sometimes difficult to accurately contour the CTV due to low soft tissue resolution of CT. The working subgroup recommends the use of MRI T2WI as a reference. Even with MRI, it is sometimes difficult to perform CTV contouring in thin women who have little adipose tissue in the pelvis. Solving this problem remains a challenge.

In conclusion, we propose that the present consensus-based guideline be used as a reference to perform appropriate contouring of the CTV primary in actual clinical practice as well as in the setting of clinical trials with IMRT for intact cervical cancer patients. The use of the present guideline in combination with the previously published guideline for the node (12) will minimize variation in the CTV contouring process. Additional discussion is still required to achieve a consensus regarding how much individualization will be permissible within the guideline. To perform appropriate IMRT, as well as accurate CTV contouring, consensus on the delineation of the OARs is important. Management of organ movement and tumor shrinkage over the treatment course represent additional challenges (28). Further substantial discussions are warranted to define the PTV margins for each CTV primary substructure. The working group needs to continue to develop additional consensus-based guidelines for the precise delivery of IMRT for patients with intact uterine cervical cancer.

## Acknowledgements

The authors thank all of the gynecologic oncologists of the JCOG Gynecologic Cancer Study Group (GCSG), Dr Yoshinori Ito and Dr Shin Fujita for their advice and expertise.

## Funding

This study was supported in part by the Grant-in-Aid for Cancer Research (20S-5) and Clinical Cancer Research (10103757) from the Ministry of Health, Labor and Welfare, Japan, and the Japan Society for the Promotion of Sciences (no. 21591614).

## Conflict of interest statement

None declared.

## References

1. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp
2. Jhingran A. Potential advantages of intensity-modulated radiation therapy in gynecologic malignancies. *Semin Radiat Oncol* 2006;16:144–51.
3. Pötter R, Fidarova E, Kirisits C, Dimopoulos J. Image-guided adaptive brachytherapy for cervix carcinoma. *Clin Oncol (R Coll Radioli)* 2008;20:426–32.
4. Mell LK, Mehrotra AK, Mundt AJ. Intensity-modulated radiation therapy use in the U.S., 2004. *Cancer* 2005;104:1296–303.
5. Mundt AJ, Lujan AE, Rotmensch J, Waggoner SE, Yamada SD, Fleming G, et al. Intensity-modulated whole pelvic radiotherapy in women with gynecologic malignancies. *Int J Radiat Oncol Biol Phys* 2002;52:1330–7.
6. Hasselle MD, Rose BS, Kochanski JD, Nath SK, Bafana R, Yashar CM, et al. Clinical outcomes of intensity-modulated pelvic radiation therapy for carcinoma of the cervix. *Int J Radiat Oncol Biol Phys* 2011;80:1436–45.
7. Kidd EA, Siegel BA, Dehdashti F, Rader JS, Mutic S, Mutch DG, et al. Clinical outcomes of definitive intensity-modulated radiation therapy with fluorodeoxyglucose-positron emission tomography simulation in patients with locally advanced cervical cancer. *Int J Radiat Oncol Biol Phys* 2010;77:1085–91.
8. Weiss E, Richter S, Krauss T, Metzelthin SI, Hille A, Pradier O, et al. Conformal radiotherapy planning of cervix carcinoma: differences in the delineation of the clinical target volume. A comparison between gynaecologic and radiation oncologists. *Radiother Oncol* 2003; 67:87–95.
9. Taylor A, Rockall AG, Reznek RH, Powell ME. Mapping pelvic lymph nodes: guidelines for delineation in intensity-modulated radiotherapy. *Int J Radiat Oncol Biol Phys* 2005;63:1604–12.
10. Taylor A, Rockall AG, Powell ME. An atlas of the pelvic lymph node regions to aid radiotherapy target volume definition. *Clin Oncol (R Coll Radiol)* 2007;19:542–50.
11. Small W, Jr, Mell LK, Anderson P, Creutzberg C, De Los Santos J, Gaffney D, et al. Consensus guidelines for delineation of clinical target volume for intensity-modulated pelvic radiotherapy in postoperative treatment of endometrial and cervical cancer. *Int J Radiat Oncol Biol Phys* 2008;71:428–34.
12. Toita T, Ohno T, Kaneyasu Y, Uno T, Yoshimura R, Kodaira T, et al. A consensus-based guideline defining the clinical target volume for pelvic lymph nodes in external beam radiotherapy for uterine cervical cancer. *Jpn J Clin Oncol* 2010;40:456–63.
13. Lim K, Small W, Jr, Portelance L, Creutzberg C, Jürgenliemk-Schulz IM, Mundt A, et al. Consensus guidelines for delineation of clinical target volume for intensity-modulated pelvic radiotherapy for the definitive treatment of cervix cancer. *Int J Radiat Oncol Biol Phys* 2011;79:348–55.
14. Haie-Meder C, Pötter R, Van Limbergen E, Briot E, De Brabandere M, Dimopoulos J, et al. Gynaecological (GYN) GEC-ESTRO Working Group. Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group (I): concepts and terms in 3D image based 3D treatment planning in cervix cancer brachytherapy with emphasis on MRI assessment of GTV and CTV. *Radiother Oncol.* 2005;74:235–45.
15. Pötter R, Haie-Meder C, Van Limbergen E, Barillot I, De Brabandere M, Dimopoulos J, et al. GEC ESTRO Working Group.Recommendations from gynaecological (GYN) GEC ESTRO working group (II): concepts and terms in 3D image-based treatment planning in cervix cancer brachytherapy-3D dose volume parameters and aspects of 3D image-based anatomy, radiation physics, radiobiology. *Radiother Oncol* 2006;78:67–77.
16. Dimopoulos JC, Schard G, Berger D, Lang S, Goldner G, Helbich T, et al. Systematic evaluation of MRI findings in different stages of treatment of cervical cancer: potential of MRI on delineation of target, pathoanatomic structures, and organs at risk. *Int J Radiat Oncol Biol Phys* 2006;64:1380–8.
17. Boehmer D, Maingon P, Poortmans P, Baron MH, Miralbell R, Remouchamps V, et al. Guidelines for primary radiotherapy of patients with prostate cancer. *Radiother Oncol* 2006;79:259–69.
18. Moore KL, Dalley AF, Agur AMR. Pelvis and perineum. In: Moore KL, Dalley AF, Agur AMR, editors. *Clinical oriented anatomy.* 6th edn. Philadelphia: Lippincott Williams & Wilkins, a Wolters Kluwer business 2010;326–438.
19. Bo WJ, Carr JJ, Krueger WA, Wolfman NT, Bowden RL. Female pelvis. In: Bo WJ, Carr JJ, Krueger WA, Wolfman NT, Bowden RL, editors. *Basic Atlas of Sectional Anatomy with Correlated Imaging.* 4th edn. Philadelphia: Elsevier Saunders 2007;313–70.

20. Baggish MS. Introduction to pelvic anatomy. In: Baggish MS, Karram MM, editors. *Atlas of Pelvic Anatomy and Gynecologic Surgery*. 2nd edn. Philadelphia: Elsevier Saunders 2006;5–60.
21. Schellhas H, Baggish MS. Radical hysterectomy. In: Baggish MS, Karram MM, editors. *Atlas of Pelvic Anatomy and Gynecologic Surgery*. 2nd edn. Philadelphia: Elsevier Saunders 2006;179–98.
22. Chen N, Min PQ, Liu ZY, Wu B, Yang KQ, Lu CY. Radiologic and anatomic study of the extraperitoneal space associated with the rectum. *Am J Roentgenol* 2010;194:642–52.
23. Chao KS, Williamson JF, Grigsby PW, Perez CA. Uterosacral space involvement in locally advanced carcinoma of the uterine cervix. *Int J Radiat Oncol Biol Phys* 1998;40:397–403.
24. Kato S, Ohno T, Tsujii H, Nakano T, Mizoe JE, Kamada T, et al. Dose escalation study of carbon ion radiotherapy for locally advanced carcinoma of the uterine cervix. *Int J Radiat Oncol Biol Phys* 2006;65:388–97.
25. Toki N, Tsukamoto N, Kaku T, Toh N, Saito T, Kamura T, et al. Microscopic ovarian metastasis of the uterine cervical cancer. *Gynecol Oncol* 1991;41:46–51.
26. Shimada M, Kigawa J, Nishimura R, Yamaguchi S, Kuzuya K, Nakanishi T, et al. Ovarian metastasis in carcinoma of the uterine cervix. *Gynecol Oncol* 2006;101:234–7.
27. Sato S, Aoki D, Kobayashi H, Saito T, Nishimura R, Nagano T, et al. Questionnaire survey of the current status of radical trachelectomy in Japan. *Int J Clin Oncol* 2011;16:141–4.
28. Lim K, Kelly V, Stewart J, Xie J, Cho YB, Moseley J, et al. Pelvic radiotherapy for cancer of the cervix: is what you plan actually what you deliver?. *Int J Radiat Oncol Biol Phys* 2009;74:304–12.

## Appendix

Other contributors of the presented work: Kazuhisa Furutani (Aichi Cancer Center, Nagoya), Naoya Murakami (National Cancer Center, Tokyo), Keiko Murofushi (Cancer Institute Hospital, Tokyo), Shin-ei Noda (Gunma University, Maebashi), Jun Itami (National Cancer Center, Tokyo), Goro Kasuya, and Takuro Ariga (University of the Ryukyus, Okinawa).

Int. J. Radiation Oncology Biol. Phys., Vol. 81, No. 4, pp. e475–e480, 2011

0360-3016/$ - see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2011.02.016

**CLINICAL INVESTIGATION** **Brain**

# COMPARISON OF CLINICAL OUTCOMES OF SURGERY FOLLOWED BY LOCAL BRAIN RADIOTHERAPY AND SURGERY FOLLOWED BY WHOLE BRAIN RADIOTHERAPY IN PATIENTS WITH SINGLE BRAIN METASTASIS: SINGLE-CENTER RETROSPECTIVE ANALYSIS

KENJI HASHIMOTO, M.D.,* YOSHITAKA NARITA, M.D.,* YASUJI MIYAKITA, M.D.,* MAKOTO OHNO, M,D.,* MINAKO SUMI, M.D.,† HIROSHI MAYAHARA, M.D.,† TAKAMASA KAYAMA, M.D.,* AND SOICHIRO SHIBUI, M.D.*

Divisions of *Neurosurgery and †Radiation Oncology, National Cancer Center Hospital, Tokyo, Japan

**Purpose:** Data comparing the clinical outcomes of local brain radiotherapy (LBRT) and whole brain RT (WBRT) in patients with a single brain metastasis after tumor removal are limited.

**Patients and Methods:** A retrospective analysis was performed to compare the patterns of treatment failure, cause of death, progression-free survival, median survival time, and Karnofsky performance status for long-term survivors among patients who underwent surgery followed by either LBRT or WBRT between 1990 and 2008 at the National Cancer Center Hospital.

**Results:** A total of 130 consecutive patients were identified. The median progression-free survival period among the patients who received postoperative LBRT ($n = 64$) and WBRT ($n = 66$) was 9.7 and 11.5 months, respectively ($p = .75$). The local recurrence rates (LBRT, 9.4% vs. WBRT, 12.1%) and intracranial new metastasis rate (LBRT, 42.2% vs. WBRT, 33.3%) were similar in each arm. The incidence of leptomeningeal metastasis was also equivalent (LBRT, 9.4% vs. WBRT, 10.6%). The median survival time for the LBRT and WBRT patients was 13.9 and 16.7 months, respectively ($p = .88$). A neurologic cause of death was noted in 35.6% of the patients in the LBRT group and 36.7% of the WBRT group ($p = .99$). The Karnofsky performance status at 2 years was comparable between the two groups.

**Conclusions:** The clinical outcomes of LBRT and WBRT were similar. A prospective evaluation is warranted. 

**Local brain radiotherapy, Whole brain radiotherapy, Single brain metastasis, Clinical outcomes, Long-term result.**

## INTRODUCTION

Whole brain radiotherapy (WBRT) has served as the standard of care for patients with brain metastases worldwide (1, 2). In patients with a single brain metastasis, postoperative WBRT has demonstrated better intracranial tumor control for both surgical lesions and nonsurgical new lesions and a lower rate of a neurologic cause of death compared with surgery alone (3). However, the addition of WBRT did not result in a survival benefit or extend the duration of the interval that the patients remained functionally independent. Some prospective trials, with the exception of one, and pooled analyses have clarified that a survival benefit for surgery followed by WBRT does exist compared with WBRT alone (1, 4–7). Other studies have also revealed that surgery followed by WBRT increased the duration of neurocognitive functional independence, as well as intracranial tumor control (4–6, 8, 9). Accordingly, surgery followed by WBRT has been the standard of care for patients with a single brain metastasis.

The median survival time of patients with brain metastases is considered to be approximately 2–7 months; favorable and unfavorable subgroups can be classified using recursive partitioning analysis (RPA) (10). However, about 2–8% of patients with brain metastasis can achieve longer survival periods (11, 12). Delayed WBRT toxicity, hypopituitarism, dementia, and memory disturbances influencing cognitive function have also been discussed, although the primary brain lesion is mainly responsible for the deterioration of functional independence (11, 13, 14).

Because WBRT is widely believed to induce dementia in patients with brain metastases, local brain RT (LBRT) as a substitute for WBRT has been widely accepted in some

Reprints requests to: Yoshitaka Narita, M.D., Division of Neurosurgery, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045 Japan. Tel: (+81) 3-3542-2511; Fax: (+81) 3-3542-3815; E-mail: yonarita@ncc.go.jp

Conflict of interest: none.

Received Sept 24, 2010, and in revised form Jan 28, 2011. Accepted for publication Feb 2, 2011.

Table 1. Patient characteristics ($n$ = 130)

| Characteristic | All patients | Range | LBRT ($n$ = 64) | WBRT ($n$ = 66) | $p$ |
|---|---|---|---|---|---|
| Age (y) | 58 | 24–87 | 58 (38–87) | 58 (24–79) | .35 |
| Karnofsky performance status | 70 | 40–100 | 70 (40–100) | 70 (40–100) | .35 |
| RPA class | II | I–III | II (I–III) | II (I–III) | .78* |
| I | 40 | 30.8 | 19 | 21 | |
| II | 55 | 42.3 | 26 | 29 | |
| III | 35 | 26.9 | 19 | 16 | |
| Cancer type (%) | | | | | .96* |
| Lung cancer | 55 | 42.3 | 29 | 26 | |
| Non–small-cell lung cancer | 54 | | 29 | 25 | |
| Small-cell lung cancer | 1 | | 0 | 1 | |
| Breast cancer | 18 | 13.8 | 9 | 9 | |
| Colorectal cancer | 14 | 10.8 | 6 | 8 | |
| Skin cancer | 6 | 4.6 | 3 | 3 | |
| Other | 37 | 28.5 | 17 | 20 | |
| Diameter of brain tumor (mm) | 38 | 10–65 | 38 (10–65) | 38 (15–60) | .57 |
| Removal status | | | | | .11 |
| Gross total removal | 124 | 95.4 | 59 | 65 | |
| Partial removal | 6 | 4.6 | 5 | 1 | |

*Abbreviations:* RPA = recursive partitioning analysis; WBRT = whole brain radiotherapy; LBRT = local brain radiotherapy,
Data presented as median, with range in parentheses.
* Chi-square test.

institutions in Japan (15). LBRT delivered by linear accelerator to the tumor bed with a margin determined using the two-field technique (opposing portal irradiation) according to a dose-fractionated schedule had been applied for the treatment of single brain metastasis after surgical removal at the National Cancer Center Hospital before September 2004. This was based on the ethics that we presumed we could treat intracranial relapse using stereotactic RT after LBRT. After discussion with neurosurgeons, radio-oncologists, and medical oncologists, however, the treatment policy was changed. WBRT has been used for the treatment of all patients with single brain metastasis after tumor removal since October 2004. A Phase I-II clinical trial of postoperative LBRT was reported, and the investigators concluded that LBRT was not a suitable substitute for WBRT (16). However, that previous study included only 12 patients, and 7 of these patients died of intracranial tumor progression. The median survival time was 7.2 months, similar to that after WBRT. Another retrospective study implied that LBRT might have a similar benefit to that of WBRT in patients with a single brain metastasis (17). Bahl *et al.* (18) reported 7 cases of postoperative LBRT, of which 4 cases recurred at the same site. These studies included only a small number of patients, and any conclusions regarding the clinical outcome of postoperative LBRT, especially compared with that of postoperative WBRT, are thus difficult to make. In the present analysis, we retrospectively compared the clinical outcomes of patients with a single brain metastasis who received surgery followed by either WBRT or LBRT.

## PATIENTS AND METHODS

### *Patient population*

From the database of the neurosurgery division at the National Cancer Center Hospital, we identified patients who had undergone brain tumor removal followed by RT between 1990 and 2008. The patients were included in the present analysis if they met the following criteria: age ≥18 years, a single brain metastasis identified by magnetic resonance imaging, and tumor removal followed by either WBRT or LBRT. The exclusion criteria were as follows: extracranial malignant lymphoma or hematological tumor; brain biopsy only; previous brain RT; surgery followed by observation, with brain RT once progression was recognized; and postoperative gamma knife or linear accelerator-based radiosurgery. All the patients who received LBRT ($n$ = 64) were treated before October 2004, and all the patients who received WBRT ($n$ = 66) were treated after October 2004.

### *Data collection and definitions of terms*

All the medical charts for the eligible patients were reviewed. To compare the clinical outcomes of postoperative WBRT and LBRT, we collected the following data:; preoperative magnetic resonance imaging; date of surgery and RT; RPA classification before surgery; Karnofsky performance status (KPS) at presentation; primary tumor site; date of recognition of local recurrence or intracranial new metastases; patterns of progression; leptomeningeal metastasis development; date of death; and neurologic cause of death. For the additional evaluation of long-term survivors (≥2 years after surgery), we also reviewed the KPS at 2 years after surgery.

Local recurrence was defined as recurrence at the surgical site. Intracranial new metastases included the detection of new brain metastases other than those occurring at the surgical site or the development of leptomeningeal metastases. Leptomeningeal metastases were diagnosed using a cytologic examination of cerebrospinal fluid.

### *Surgery and RT*

The surgical indications for single brain metastasis were generally as follows: tumor diameter ≥30 mm or a tumor diameter of <30 mm with neurologic dysfunction.

Whole brain RT was administered through two lateral ports covering the brain and meninges to the foramen magnum. Normally, WBRT was delivered using a 4-MV or 6-MV linear accelerator at

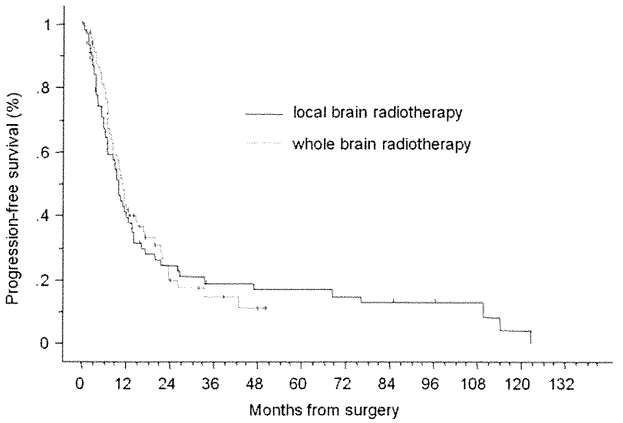



Fig. 1. Progression-free survival for patients with local brain radiotherapy (black line) and whole brain radiotherapy (dashed line).

a total dose of 30 Gy in 10 fractions or 37.5 Gy in 15 fractions. Patients who received LBRT underwent computed tomography simulation in the supine position. The clinical target volume consisted of the tumor cavity plus a 1.5-cm margin, and the planning target volume was created by expanding the clinical target volume by 0.5 cm. LBRT was administered using a 6-MV linear accelerator to the tumor bed using a two-field technique according to a dose-fractionated schedule. Normally, LBRT was delivered at a total dose of 50 Gy in 25 fractions.

### *Statistical analysis*

Postoperative differences in local recurrence, intracranial new metastases, the development of leptomeningeal metastases, and neurologic cause of death were compared between the WBRT and LBRT groups using the Fisher exact test. Numeric data, including RPA, KPS, and age, were compared using the Mann-Whitney *U* test. Progression-free survival was defined as the interval between the date of surgery to the date of the recognition of local recurrence or intracranial new metastases. Death was treated as an event, and the absence of disease progression was treated as a censored observation on the last day of follow-up. Overall survival was defined as the interval from the date of surgery to the date of death. Patients who were lost to follow-up were treated as a censored observation on the last day of follow-up. Univariate and multivariate analyses using the Cox proportional hazard model were performed to identify relevant factors affecting survival. The numeric factors analyzed in the Cox analyses were dichotomized according to the median number. All statistical analyses were performed using StatView, version 5.0 (SAS Institute, Tokyo, Japan).

## RESULTS

Of the 421 surgical cases, we identified 130 patients who met the eligibility criteria. The characteristics of these patients are listed in Table 1. Of the 130 patients, 66 had received postoperative WBRT and 64 had received postoperative LBRT. Of the 66 patients who had received WBRT, 34 (51.5%) were treated to a dose of 30 Gy delivered in 10 fractions, and 31 (47.0%) were treated to a dose of 37.5 Gy delivered in 15 fractions. Of the 64 patients who received LBRT, 57 (89.1%) were treated to a dose of 50 Gy in 25 fractions, and 7 were treated with a variety of dose-fractionation schedules (24 Gy in 12 fractions to 60 Gy in 30 fractions).

The median progression-free survival period for the patients who received postoperative LBRT and WBRT was 9.7 and 11.5 months, respectively ($p$ = .75; Fig. 1). The patients who underwent LBRT and WBRT developed 33 and 30 recurrences, respectively. The local recurrence rates (9.4% vs. 12.1%) and intracranial new metastases rates (42.2% vs. 33.3%) were not significantly different between the LBRT and WBRT groups (Table 2). The incidence of leptomeningeal metastases in patients receiving LBRT and WBRT was 9.4% and 10.6%, respectively ($p$ = .99).

The median survival time for patients who received postoperative LBRT and WBRT was 13.9 and 16.7 months, respectively ($p$ = .88; Fig. 2). Of the 64 patients who received LBRT and the 66 patients who received and WBRT, 59 and 49 died, respectively. A neurologic cause of death was noted in 35.6% of the patients in the LBRT group and 36.7% of the patients in the WBRT group ($p$ = .99; Table 2). Univariate analyses revealed that only the RPA classification correlated significantly with survival (hazard ratio [HR], 0.436; $p$ = .002). In particular, RT (LBRT vs. WBRT) did not correlate with survival (HR, 1.031; $p$ = .88; Table 3). Multivariate analyses revealed that RPA was the only significant factor associated with survival (HR, 0.399; $p$ = .001). Neither LBRT nor WBRT was related to survival (HR, 0.933; $p$ = .74; Table 4).

Table 2. Patterns of treatment failure in patients who received WBRT and LBRT

| Variable | LBRT ($n$ = 64) | WBRT ($n$ = 66) | |
|---|---|---|---|
| Total recurrences identified *(n)* | 33 | 30 | *p* |
| Local recurrence | 6 (18.2) | 8 (26.7) | .61 |
| Distant metastasis | 27 (81.8) | 22 (73.3) | .61 |
| Development of leptomeningeal metastases *(n)* | 6 | 7 | .99 |
| Total deaths identified *(n)* | 59 | 49 | |
| Neurologic cause of death | 21 (35.6) | 18 (36.7) | .98* |
| Other | 21 (35.6) | 17 (34.7) | |
| Unknown | 17 (28.8) | 15 (30.6) | |

*Abbreviations:* WBRT = whole brain radiotherapy; LBRT = local brain radiotherapy.
Data in parentheses are percentages.
* Chi-square test.

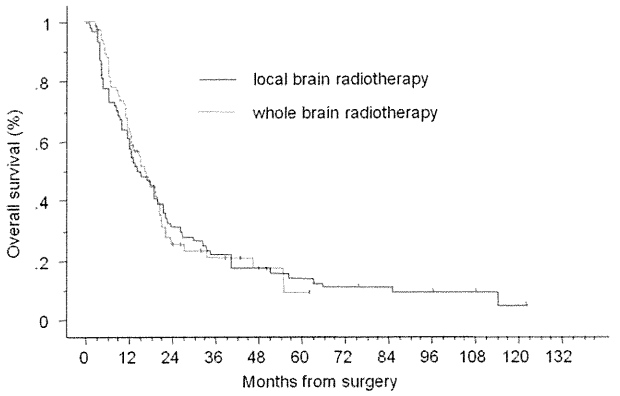



Fig. 2. Overall survival in patients with local brain radiotherapy (black line) and whole brain radiotherapy (dashed line).

We further analyzed the patterns of RT after recurrence in patients who received either postoperative LBRT or WBRT. Of the 33 patients who developed recurrences after postoperative LBRT, additional RT was performed in 15 (45.5%). Of the 15 patients, 6 underwent gamma knife or linear accelerator-based radiosurgery. LBRT was performed in 5 patients, and 4 received WBRT. Of the 30 patients who developed recurrences after postoperative WBRT, 16 (53.3%) received additional RT. Of the 16 patients, 13 received gamma knife or linear accelerator-based radiosurgery, and 3 received LBRT.

Among the patients who survived for >2 years, we compared the KPS at 2 years after surgery. A total of 20 patients who had received postoperative LBRT and 13 who had received postoperative WBRT were identified. The median KPS score at 2 years for these patients in the LBRT and WBRT groups was 80 (range, 60–100) and 80 (range, 60–100; $p = .99$), respectively. Of the 20 patients who had received LBRT, 9 experienced relapse in a local lesion, 2 had focal signs without relapse, which might have indicated radiation necrosis, and 7 had been well without relapse. For 2 other patients, this information was not available.

## DISCUSSION

We have revealed the clinical outcomes of postoperative LBRT among patients with single metastasis and compared them with those of patients who underwent postoperative WBRT. The clinical outcomes, including progression-free survival, overall survival, local recurrence, intracranial new metastases, development of leptomeningeal metastases, and neurologic cause of death, were not significantly different between the two groups. In an analysis of relapse patterns, the patients treated with LBRT tended to have a lower probability of developing local recurrence (9.4% vs. 12.1%) and a greater probability of developing intracranial new metastases (42.2% vs. 33.3%), although these values were not significantly different. The probability of developing leptomeningeal metastases was also similar in each group (9.4% vs. 10.6%).

Previous reports have indicated that the addition of WBRT after tumor removal significantly reduces the local recurrence rate (3, 9). However, approximately 6–50% of patients develop relapses at new intracranial sites in the brain (5, 9, 19). Furthermore, about 20–30% of patients with brain metastasis die of neurologic causes even if a radiation boost has been added using stereotactic radiosurgery to increase local control, although the presence of extracranial lesions is the strongest factor for predicting survival (7, 20, 21). In our study, intracranial new metastases were predominant in both groups. The frequency of intracranial recurrence (new local and intracranial metastases) was somewhat greater than in previous series, although the rate of a neurologic cause of death was equivalent. Importantly, the patterns of treatment failure were similar in the LBRT and WBRT groups. Muacevic *et al.* (22) insisted that postoperative WBRT should be applied in patients with a single brain metastasis to destroy so-called micrometastases, based on the results of their randomized trial. They compared patients with a small single metastasis who received either surgery plus WBRT or gamma knife surgery alone. Their sample size was underpowered, although the risk of intracranial new metastases seemed to be lower in the WBRT cohort. To date, no randomized trials comparing the clinical outcomes of postoperative WBRT and postoperative gamma knife or linear accelerator-based radiosurgery, or LBRT have been reported.

We have demonstrated a similar efficacy for LBRT and WBRT. WBRT has problems in terms of delayed toxicity developing leukoencephalopathy, although the number of long-term survivors with brain metastasis seems to be somewhat low (11, 12). LBRT might be beneficial with regard to the protection of normal brain tissue. We compared the KPS

Table 3. Univariate analyses regarding survival

| Variable | HR | 95% CI | *p* |
|---|---|---|---|
| RT (LBRT vs. WBRT) | 1.031 | 0.698–1.523 | .88 |
| RPA classification | | | |
| I vs. III | 0.436 | 0.259–0.733 | .002 |
| II vs. III | 0.808 | 0.514–0.127 | .35 |
| Removal status (gross total removal vs. partial removal) | 0.948 | 0.385–2.334 | .91 |
| Tumor diameter (≥38 vs. <38 mm) | 1.053 | 0.718–1.543 | .79 |
| Cancer type (lung cancer vs. other) | 0.694 | 0.470–1.025 | .062 |

*Abbreviations:* RT = radiotherapy; HR = hazard ratio; CI = confidence interval; other abbreviations as in Table 1.

Table 4. Multivariate analyses regarding survival

| Variable | HR | 95% CI | *p* |
|---|---|---|---|
| RT (LBRT vs. WBRT) | 0.933 | 0.614–1.416 | .743 |
| RPA classification | | | |
| I vs. III | 0.399 | 0.232–0.688 | .001 |
| II vs. III | 0.736 | 0.455–1.191 | .22 |
| Removal status (gross total removal vs. partial removal) | 0.622 | 0.239–1.615 | .33 |
| Tumor diameter (≥38 vs. <38 mm) | 0.852 | 0.559–1.297 | .45 |
| Cancer type (lung cancer vs. other) | 0.662 | 0.438–1.001 | .05 |

Abbreviations as in Tables 1 and 3.

at 2 years to examine any delayed toxicity. Because of the nature of the present retrospective study, the detailed neurocognitive function or quality of life of the patients could not be identified. Among the long-term survivors, however, the KPS was preserved in both treatment groups. Thus, LBRT might be indicated for elderly patients at risk of developing dementia if LBRT has the same ability to control primary brain tumors, which is considered to be the main factor affecting neurocognitive function (14).

The present study had some limitations because of its retrospective nature. First, the radiation dose varied. About 90% of the LBRT patients received a dose of 50 Gy delivered in 25 fractions, and approximately 50% of the WBRT patients received a dose of 30 Gy delivered in 10 fractions; the others received a dose of 37.5 Gy delivered in 15 fractions. According to the summary by Tsao *et al.* (1), no differences in terms of survival or neurocognitive function were observed among the various dose-fraction schedules of WBRT. Second, the present study was a historical case-control study comparing LBRT and WBRT. Patients at risk of developing multiple metastases might have undergone WBRT during the period before 2004, when we started performing WBRT as the standard of care. Thus, the patients who were treated with LBRT might have had better general condition compared with the patients who were treated with WBRT. We compared the baseline characteristics of each treatment arm and used multivariate analyses to reduce any potential biases.

## CONCLUSIONS

We have demonstrated the clinical efficacy of LBRT compared with WBRT on a large scale. The clinical outcomes, including progression-free survival, overall survival, patterns of treatment failure, development of leptomeningeal metastases, and a neurologic cause of death, were similar in both treatment groups. The KPS at 2 years was also similar when the two groups were compared. This result should be evaluated in a prospective manner.

## REFERENCES


1. Tsao MN, Lloyd NS, Wong RK, *et al.* Radiotherapeutic management of brain metastases: A systematic review and meta-analysis. *Cancer Treat Rev* 2005;31:256–273.
2. Coia LR. The role of radiation therapy in the treatment of brain metastases. *Int J Radiat Oncol Biol Phys* 1992;23: 229–238.
3. Patchell RA, Tibbs PA, Regine WF, *et al.* Postoperative radiotherapy in the treatment of single metastases to the brain: A randomized trial. *JAMA* 1998;280:1485–1489.
4. Noordijk EM, Vecht CJ, Haaxma-Reiche H, *et al.* The choice of treatment of single brain metastasis should be based on extracranial tumor activity and age. *Int J Radiat Oncol Biol Phys* 1994;29:711–717.
5. Patchell RA, Tibbs PA, Walsh JW, *et al.* A randomized trial of surgery in the treatment of single metastases to the brain. *N Engl J Med* 1990;322:494–500.
6. Vecht CJ, Haaxma-Reiche H, Noordijk EM, *et al.* Treatment of single brain metastasis: Radiotherapy alone or combined with neurosurgery? *Ann Neurol* 1993;33:583–590.
7. Mintz AH, Kestle J, Rathbone MP, *et al.* A randomized trial to assess the efficacy of surgery in addition to radiotherapy in patients with a single cerebral metastasis. *Cancer* 1996;78:1470–1476.
8. Rades D, Fehlauer F, Schild S, *et al.* [Treatment for central neurocytoma: A meta-analysis based on the data of 358 patients]. *Strahlenther Onkol* 2003;179:213–218.
9. Nieder C, Astner ST, Grosu AL, *et al.* The role of postoperative radiotherapy after resection of a single brain metastasis: Combined analysis of 643 patients. *Strahlenther Onkol* 2007;183: 576–580.
10. Gaspar L, Scott C, Rotman M, *et al.* Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. *Int J Radiat Oncol Biol Phys* 1997;37:745–751.
11. Chao ST, Barnett GH, Liu SW, *et al.* Five-year survivors of brain metastases: A single-institution report of 32 patients. *Int J Radiat Oncol Biol Phys* 2006;66:801–809.
12. Lutterbach J, Bartelt S, Ostertag C. Long-term survival in patients with brain metastases. *J Cancer Res Clin Oncol* 2002; 128:417–425.
13. Sheline GE, Wara WM, Smith V. Therapeutic irradiation and brain injury. *Int J Radiat Oncol Biol Phys* 1980;6: 1215–1228.
14. Aoyama H, Tago M, Kato N, *et al.* Neurocognitive function of patients with brain metastasis who received either whole brain radiotherapy plus stereotactic radiosurgery or radiosurgery alone. *Int J Radiat Oncol Biol Phys* 2007;68:1388–1395.
15. Ueki K, Matsutani M, Nakamura O, *et al.* Comparison of whole brain radiation therapy and locally limited radiation therapy in the treatment of solitary brain metastases from non-small cell lung cancer. *Neurol Med Chir (Tokyo)* 1996;36:364–369.

16. Coucke PA, Zouhair A, Ozsahin M, *et al.* Focalized external radiotherapy for resected solitary brain metastasis: Does the dogma stand? *Radiother Oncol* 1998;47:99–101.
17. Iwadate Y, Namba H, Yamaura A. Whole-brain radiation therapy is not beneficial as an adjuvant therapy for brain metastases compared with localized irradiation. *Anticancer Res* 2002;22: 325–330.
18. Bahl G, White G, Alksne J, *et al.* Focal radiation therapy of brain metastases after complete surgical resection. *Med Oncol* 2006;23:317–324.
19. Smalley SR, Schray MF, Laws ER Jr., *et al.* Adjuvant radiation therapy after surgical resection of solitary brain metastasis: Association with pattern of failure and survival. *Int J Radiat Oncol Biol Phys* 1987;13:1611–1616.
20. Andrews DW, Scott CB, Sperduto PW, *et al.* Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: Phase III results of the RTOG 9508 randomised trial. *Lancet* 2004;363:1665–1672.
21. Aoyama H, Shirato H, Tago M, *et al.* Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: A randomized controlled trial. *JAMA* 2006;295:2483–2491.
22. Muacevic A, Wowra B, Siefert A, *et al.* Microsurgery plus whole brain irradiation versus gamma knife surgery alone for treatment of single metastases to the brain: A randomized controlled multicentre phase III trial. *J Neurooncol* 2008;87:299–307.

Japanese Journal of Clinical Oncology Advance Access published April 23, 2012

JJCO Japanese Journal of Clinical Oncology

*Jpn J Clin Oncol 2012*
*doi:10.1093/jjco/hys055*

**Case Report**

# Successful Control of Intractable Hypoglycemia Using Radiopharmaceutical Therapy with Strontium-89 in a Case with Malignant Insulinoma and Bone Metastases

**Atsushi Naganuma[1,2], Hiroshi Mayahara[3], Chigusa Morizane[1,*], Yuriko Ito[1,4], Atsushi Hagihara[1,5], Shunsuke Kondo[1], Hideki Ueno[1], Jun Itami[3] and Takuji Okusaka[1]**

[1]Hepatobiliary and Pancreatic Oncology Division, National Cancer Center Hospital, Tokyo, [2]Department of Gastroenterology, Takasaki General Medical Center, National Hospital Organization, Gunma, [3]Radiation Oncology Division, National Cancer Center Hospital, Tokyo, [4]Department of Clinical Oncology, Yamagata University School of Medicine, Yamagata and [5]Department of Hepatology, Osaka City University Graduate School of Medicine, Osaka, Japan

*For reprints and all correspondence: Chigusa Morizane, Hepatobiliary and Pancreatic Oncology Division, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. E-mail: cmorizan@ncc.go.jp

Received December 21, 2011; accepted March 22, 2012

This report describes the case of a 57-year-old woman with liver and bone metastases from malignant insulinoma, who was afflicted with severe hypoglycemia. Treatment of the liver metastases using octreotide, diazoxide and transarterial embolization failed to raise her blood glucose level and she required constant glucose infusion (about 1000 kcal/day) and oral feeding (about 2200 kcal/day) to avoid a hypoglycemic attack. Subsequently, 110 MBq (2.0 MBq/kg) of strontium-89 were administered by intravenous injection. Three weeks after the strontium-89 injection, we could reduce the dose of constant glucose infusion while maintaining a euglycemic status. Six weeks after the injection, the constant glucose infusion was discontinued. Although strontium-89 therapy is indicated for patients with multiple painful bone metastases, it was also useful as a means of inhibiting tumor activity and controlling hypoglycemia in this case. To our knowledge, this is the first report to provide evidence that strontium-89 can be useful in controlling intractable hypoglycemia in patients with malignant insulinoma with bone metastases.

*Key words: strontium-89 – malignant insulinoma – bone metastases*



## INTRODUCTION

Insulinomas are rare tumors that arise from the pancreatic islet cells that produce insulin. Approximately 5–10% of the insulinomas are cancerous (1). It is often difficult to control inappropriate insulin secretion and hypoglycemia in patients with a malignant insulinoma. Although surgery is indicated for symptomatic or malignant insulinoma, only medical therapy is suggested for unresectable patients (2). Some cases suffer from intractable hypoglycemia as a result of the limited efficacy of medical therapy. We report here on the case of a 57-year-old woman with a malignant insulinoma and bone metastases in whom intractable hypoglycemia was successfully controlled by using radiopharmaceutical therapy with strontium (Sr)-89.

## CASE REPORT

In March 2002, a 57-year-old woman experienced frequent hypoglycemic attacks and was diagnosed as having an insulinoma of the pancreas tail at a previous hospital. She

underwent surgery including a distal pancreatectomy and splenectomy at the previous hospital. The maximum diameter of the surgically removed tumor was 10 cm. The histopathological findings revealed a pancreas islet cell carcinoma. The tumor had directly invaded the spleen and protruded into the splenic vein and pancreatic duct. The surgical resection stump was negative.

In February 2005, multiple liver metastases were detected and the patient was referred to our hospital. Then, she received a partial hepatectomy for multiple liver metastases in our hospital. The histopathological findings of resected specimen showed a low-grade endocrine cell carcinoma. The immunohistochemical staining showed positive for chromogranin A and synaptophysin, but it showed negative for insulin. In July 2006, she underwent a second partial hepatectomy for recurrent multiple liver metastases. Histopathological examination of the liver metastases showed similar findings to the first liver segmental resection.

In December 2008, multiple liver metastases and multiple bone metastases including lumbar vertebrae and iliac bone were detected. In March 2009, she started zoledronic acid hydrate treatment for the bone metastases, but it was discontinued because of severe jaw pain suggesting the possibility of mandibular osteonecrosis. In November 2009, the patient experienced a hypoglycemic attack again. The patient was hospitalized to control her serum glucose level. The laboratory data obtained at admission are shown in Table 1. Regarding the serum hormonal level, the insulin level was slightly elevated but the glucagon level was not elevated. The level of neuron-specific enolase was slightly elevated. The patient underwent short-acting somatostatin analogs for 14 days to control the serum glucose level due to their antiproliferation effect. After having confirmed that there was no worsening of the hypoglycemia symptoms, we changed her treatment to a long-acting somatostatin analog (Sandostatin-LAR; Novartis Pharmaceuticals). However, hypoglycemia occurred frequently (Fig. 1) even after the initiation of octreotide therapy. The patient refused to continue the octreotide therapy because her hypoglycemic attacks had not improved. The hypoglycemia persisted after the discontinuation of octreotide. Next, diazoxide was administered with no effect but with the side effects of significant edema and weight gain. We decided to undertake transarterial embolization (TAE) to necrotize the liver metastases and

**Table 1.** Laboratory data upon the first admission after the experience of a hypoglycemic attack

| | Actual level | Normal level | | Actual level | Normal level |
|---|---|---|---|---|---|
| Hematology | | | Tumor markers | | |
| Leukocyte (per $mm^3$) | 10 200 | (3900–6300) | CEA (ng/ml) | 2.5 | (<5) |
| Hemoglobin (g/dl) | 11.9 | (11.3–14.9) | CA19–9 (U/ml) | 12 | (<37) |
| Platelet (per $mm^3$) | $39 \times 10^4$ | ($12.5–37.5 \times 10^4$) | NSE (ng/ml) | 18.5 (H) | (<15) |
| Biochemistry | | | ProGRP (pg/ml) | 37.7 | (<46) |
| Total protein (g/dl) | 8.0 | (6.3–8.3) | Hormones | | |
| Albumin (g/dl) | 3.6(L) | (3.7–5.2) | Insulin (mIU/ml) | 12.9 (H) | (1.84–12.2) |
| Total bilirubin (mg/dl) | 0.6 | (0.3–1.2) | Gastrin (pg/ml) | 82 | (<200) |
| Fasting glucose (mg/dl) | 70 | (69–104) | Glucagon (pg/ml) | 120 | (50–150) |
| BUN (mg/dl) | 14 | (8–22) | Urine | | |
| Creatine (mg/dl) | 0.6 | (0.4–0.7) | pH | 6.0 | (4.6–7.5) |
| Sodium (mEq/l) | 138 | (138–146) | Protein | (—) | |
| Potassium (mEq/l) | 4.2 | (3.6–4.9) | Sugar | (—) | |
| Chloride (mEq/l) | 104 | (99–109) | Blood | (—) | |
| Calcium (mg/dl) | 9.0 | (8.7–10.3) | | | |
| Amylase (IU/l) | 64 | (42–132) | | | |
| ALP (IU/l) | 440 (H) | (115–359) | | | |
| AST (IU/l) | 16 | (13–33) | | | |
| ALT (IU/l) | 9 | (6–27) | | | |
| LDH (IU/l) | 174 | (119–229) | | | |
| γ-GTP (IU/l) | 25 | (10–47) | | | |

BUN, blood urea nitrogen; ALP, alkaline phosphatase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; γ-GTP, γ-glutamyltransferase; APTT, activated partial thromboplastin time; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; NSE, neuron-specific enolase; Pro-GRP, pro-gastrin-releasing peptide; (H), high; (L), low.

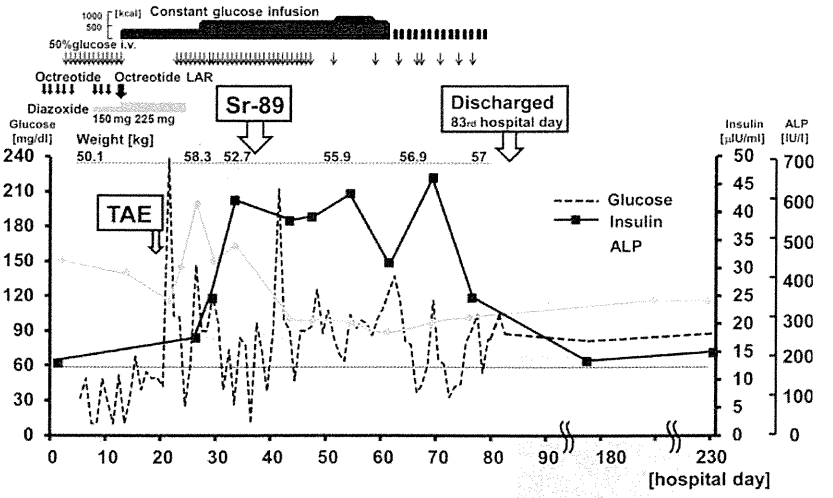



**Figure 1.** Clinical course. Three weeks after the strontium-89 injection, the patient was weaned from the constant glucose infusion while successfully maintaining euglycemia and lower circulating insulin levels. About 6 weeks after the injection, the constant glucose infusion was completely stopped, even though the previous treatment had failed.

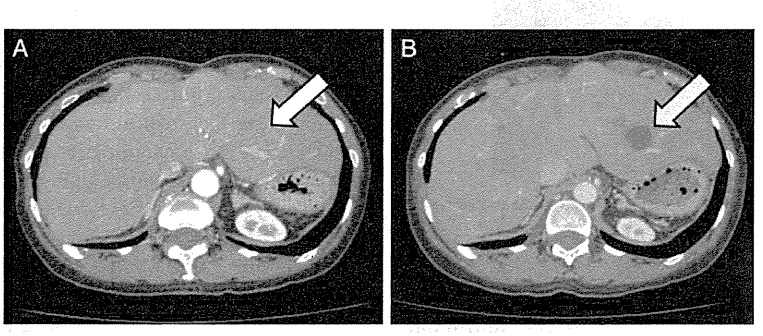



**Figure 2.** Liver metastases were observed using enhanced computed tomography (A and B, arrow). The liver metastases did not exhibit remarkable hypervascular staining in computed tomography before transarterial embolization (A, arrow), but successful necrotization was achieved using transarterial embolization, as shown in this enhanced computed tomographic imaging 1 week after the treatment (B, arrow). However, the treatment failed to increase the patient's blood glucose level.

prevent the hypoglycemia. TAE was performed on the 20th hospital day. We succeeded in necrotizing the metastases, as shown in Fig. 2. However the hypoglycemia persisted, and then the patient required constant glucose infusions and oral feeding to avoid a hypoglycemic attack (Fig. 1). As shown in Fig. 3A and B, bone scintigraphy revealed a worsening of the bone metastases, compared with images obtained 1 year previously.

$^{89}$Sr is a novel radiopharmaceutical agent used for the palliation of bone pain from multiple osseous metastases (3). The patient suffered from slight lumbago as a result of the bone metastases, so we attempted to use $^{89}$Sr to alleviate her pain and to control her hypoglycemia. In the computed tomography (Fig. 4), the bone metastases showed osteoplastic findings that suggested high sensitivity to $^{89}$Sr (4). A 110-MBq dose (2 MBq per kg) of $^{89}$Sr was administered by intravenous injection on the 37th hospital day (Fig. 1). One week after the injection, the serum level of alkaline phosphatase was normalized. We were able to confirm the accumulation of $^{89}$Sr in metastatic foci that corresponded to bone scintigraphy by using gamma camera (Fig. 3C). Three weeks after the $^{89}$Sr injection, we were able to reduce the dose of constant glucose infusion while maintaining a euglycemic status. Six weeks after the injection, she stopped constant glucose infusion and the bone pain was relieved (Fig. 1). The patient was discharged on the 83rd hospital day. Two months after the $^{89}$Sr injection, she was hospitalized again for 3 weeks because of a transient liver dysfunction due to a hepatitis C virus infection. Liver dysfunction was improved using conservative treatment. In December 2010, no progression of bone metastases was seen on bone scintigraphy, and the hypoglycemic control was consistently good. The patient received a second $^{89}$Sr treatment 1 year after the first $^{89}$Sr treatment because of the recurrence of bone pain. After the $^{89}$Sr treatment, the bone pain has remained improved until the time of writing. Local